THE BRITISH JOURNAL OF OPHTHALMOLOGY

EDITED BY

THE ROYAL LONDON OPHTHALMIC HOSPITAL REPORTS
THE OPHTHALMIC REVIEW AND THE OPHTHALMOSCOPE

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Annual Subscription Three Guineas [illegible] Single Copy [illegible]

[illegible] published together with "Ophthalmic [illegible]

Ophthalmology" [illegible]

All [illegible] to be addressed to the Secretary of the Editorial Committee, [illegible]

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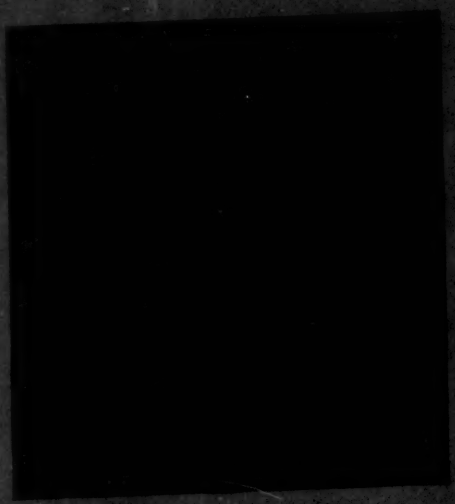

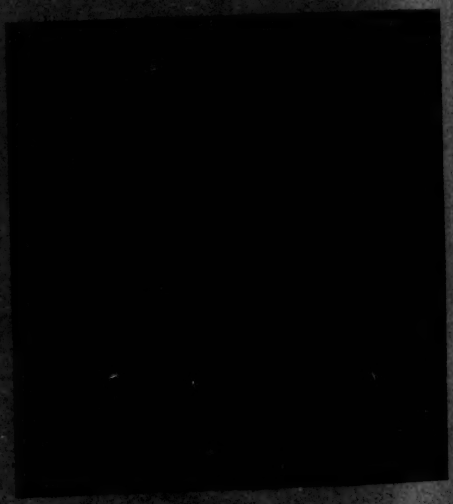

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THE BRITISH JOURNAL

OF

OPHTHALMOLOGY

NOVEMBER, 1949

COMMUNICATIONS

VON HIPPEL-LINDAU DISEASE*

Clinical and Pathological Report of a Case

BY

I. C. MICHAELSON *and* J. HILL

GLASGOW

IT IS not often that an opportunity presents itself for the histological study of a case of von Hippel's disease; and it is even more unusual to combine this with microscopic examination of one of the tumours in the central nervous system, described by Lindau. The case here reported offers both opportunities, and may help to throw some light on the pathogenesis of the v. Hippel-Lindau complex.

The patient, a man aged 24 years, was seen for the first time at the Glasgow Eye Infirmary on March 22, 1948, complaining of defective vision in the right eye, and repeated attacks of epistaxis for a number of years. For one month

* Received for publication May 28, 1949.

there had been severe intermittent left occipital headache, especially severe in the mornings, and once or twice associated with projectile vomiting. Seven weeks before admission he had an attack of giddiness leading to collapse.

In the right eye (Fig. 1) the ophthalmoscope showed a large grey globular detachment of the retina in the lower nasal quadrant, and several smaller detachments above. The principal retinal vessels were much dilated and tortuous. There was diffuse white opacity of much of the detached retina. Transillumination

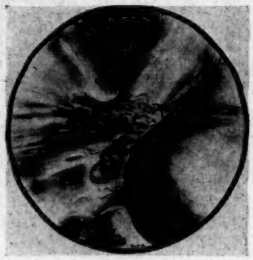

FIG. 1.

v. Hippel—Lindau disease. Ophthalmoscopic examination of right eye before excision. Extensive retinal detachment. Distension and tortuosity of vessels. New-built vessels. Gliosis.

gave an indefinite shadow in the lower area. The tension of the eye was normal. The fundus of the left eye was normal.

General examination revealed no abnormality of blood pressure, or of the circulatory, respiratory, gastro-intestinal or nervous systems. W.R. was negative. There were no cutaneous angiomata, and no X-ray evidence of intracranial disease.

The right eye was excised on April 16, and on April 21 he was transferred to the neuro-surgical unit at Killearn Hospital.

Operation (Dr. Schorstein) disclosed a cerebellar tumour, the removal of which was followed by deep X-ray therapy. The patient made an excellent recovery. The tumour was diagnosed as a haemangioblastoma.

PATHOLOGY

Serial sections of the retina of the right eye were cut in paraffin in the 12 to 6 o'clock meridian, and stained with haematoxylin and eosin, Mallory, van Gieson and Weigert's elastic tissue stain.

In a general survey the retina exhibits great distortion, variations in thickness, and degeneration of the retinal layers. At no part of the fundus is there a completely normal retina. In the least affected parts, about 5 mm. above and below the macula, there is destruction of the rods and cones and confusion of the nuclear and internuclear layers. In the more central area there is extensive destruction of the nuclear and ganglion cell layers, the retina for the most part consisting of coarse bands of neuroglia passing obliquely or anteroposteriorly through its whole thickness.

There are many *cysts* (Fig. 2) large and small, round and irregular in shape, empty or otherwise. The contents of the cysts consist of large cells with scanty pigment granules, apparently derivatives of the hexagonal pigment cells. There are so many gradations between the round, clearly defined cavities and the ragged fissures that it is difficult to say which are true cysts and which are the result of the tendency to cleavage of the retina along the lines of the glial framework.

FIG. 2.

Degenerate retina. A fibro-cellular septum which projects into a large cyst contains endothelial cells.

FIG. 3.

A large nodule, composed mainly of glial and endothelial cells. Small vessels are forming. The nodule occupies the whole thickness of the retina. In the upper part of the photograph a neighbouring nodule has undergone hyalinisation of the matrix.

FIG. 4.

v. Hippel—Lindau Disease. Diffuse gliosis and multiplication of small vessels. Hyaline change in the matrix of the tumour tissue.

FIG. 5.

Two large vessels in the degenerate retina. The coats of the vessel walls are not distinguishable, and the wall of one vessel (vein?) contains several intra-mural vessels.

Dark clumps of *pigment cells* are deposited in irregular fashion, especially in the posterior part of the retina, but also as far forward as the nerve fibre layer. They often form dark deposits in the walls of vessels or cysts.

Pseudo-membranes of varying thickness are found attached to both anterior and posterior surfaces of the retina. At some points these are in continuity with

substantial homogeneous masses (hyaline?) in the retina, some of which contain blood vessels.

A striking feature of this part of the retina is the presence of fibro-cellular *nodules*, of varying size and situated in any or all of the layers (Fig. 3). There are also more diffuse patches of somewhat similar fibro-cellular structure (Fig. 4).

In sections just temporal to the disc the principal vessels are recognised as an upper and lower pair, corresponding with the normal superior and inferior temporal vessels. Both artery and vein are expanded and have thickened walls. In some parts there is lymphocytic infiltration of the wall. Here and there additional large vessels appear, probably produced by expansion of subsidiary branches. Large vessels have not only encroached on the deep and superficial layers, but at several points are seen to have perforated the anterior and the posterior limiting membranes.

Some vessels are seen which show little change from the normal histology, but in most there is not only thickening but also a varying degree of hyaline change.

One or two of the larger vessels show an incomplete differentiation of their coats; the walls contain some scattered endothelial cells, and here and there are intramural vessels, or *vasa vasorum*, similar to those described by Loewenstein (1947) (Fig. 5).

The gross changes so far described are largely degenerative, and do not in themselves offer any guide to the pathogenesis of the condition. For this we have to turn to the nodular lesions already mentioned. It seems to be here that we find a clue to the earliest stage in this tumour formation. The nodules vary greatly in size, the largest occupying the whole depth of the thickened retina

FIG. 6.

A cluster of endothelial cells, deep in the retina, resembles a giant-cell.

FIG. 7.

Another cluster of endothelial cells, in the anterior part of the retina, shows the formation of endothelium-lined vessels.

(Fig. 3). At a number of points we find clusters of endothelial cells, as small as 30μ in diameter, with a strong resemblance to giant-cells (Fig. 6). In some of these clusters clear vacuoles appear, lined with endothelium (now definitely blood-vessels) (Fig. 7). These increase in number and size, while the matrix in which they are embedded increases in amount and is seen to be composed of neuroglia together with endothelial cells.

These changes apparently represent a series of phases in the growth of the nodule; and a further change, which would appear to be the next stage in the process, is the gradual hyalinisation of the matrix. This begins in the central

part (Fig. 8) and extends gradually through the rest of the nodule, until the matrix loses its fibro-cellular character, and the vessels are seen to be embedded in a homogeneous waxy-looking mass (Fig. 9) which stains faintly red with eosin, blue with Mallory, and crimson with van Gieson. With Mallory a certain fibrillary structure is indicated.

A similar series of changes takes place more diffusely in this part of the retina. We have noted that much of the degenerative retina is composed of coarse bands of glial tissue. These are associated here and there with endothelial cells which do not group themselves in nodular form. This "gliosis" gives place to a hyaline material, sometimes with, and sometimes without enclosed capillary vessels.

In all these parts, both in the nodules and in the intervening tissue, the proportion of vessels to matrix varies a good deal. Sometimes large vessels join up to form a cavernous plexus, elsewhere the vessels may be few and of capillary structure, buried in a mass of "hyaline" tissue. Here and there we find a very small nodule of the endotheliomatous tissue in the wall of a large cyst, or in a

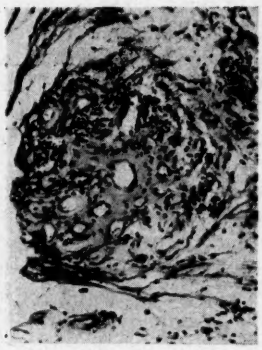

FIG. 8.

A large nodule, about 250μ in diameter, in the posterior part of the retina. It is full of small vessels. The matrix is becoming hyaline.

FIG. 9.

A large angiomatous nodule in which the vessel walls and the supporting matrix are almost completely hyaline.

septum of connective tissue projecting into the cyst (Fig. 2). This may have some relation to the haemangiomatous cysts in other organs discovered in Lindau's cases.

The aforementioned hyaline changes, which are a pronounced feature of most of the sections, are of interest, but their significance is not clear. The hyaline material appears:—(1) as a result of the progressive change in the fibro-cellular matrix of the nodules, as well as in the intervening tissues (Fig. 8); (2) as a result of a pathological change in the thickened walls of the retinal vessels, both small and large (Fig. 9); and (3) as hyaline masses at all depths in the retina and on its anterior surface, some of which contain a few small vessels while others are completely avascular (Fig. 4). It may be taken as a degenerative change in the overgrown neuroglial tissue of the retina, probably the latest phase in the growth of the retinal tumour.

THE CEREBELLAR TUMOUR

The histological character of the portion of the cerebellar tumour available to us differs from that of the retinal growth, (1) in the absence of nodular formations; (2) in the absence of the degenerative changes, such as cyst-formation,

gliosis and hyalinisation, as seen in the retinal tumour. Here and there we find clusters of unorganised endothelial cells resembling giant-cells, some of which contain one or two small vascular channels lined with endothelium, and the tumour tissue in general consists of a light matrix of endothelial and supporting cells containing many blood-channels of widely varying size, lined with flattened or almost cubical endothelial cells. In some parts a free inter-communication between neighbouring vessels gives the tumour a cavernous character.

Incidentally, sections from a case of cavernous angioma of the eyelid, for which we are indebted to Professor A. Loewenstein, show appearances almost identical with those in Fig. 8.

Comment

The problem of the isolation and identification of the initial lesion is one which is common to all retinal diseases of " massive exudative " type; for the eyes in these cases are seldom submitted to pathological examination until marked secondary changes have occurred. In this country the first important contribution to our knowledge of the disease was that of Collins (1894), who had the opportunity of studying the histology of an eye which had been clinically examined and described two years earlier by Wood (1892), and subsequently of examining both eyes of this patient's sister. In each of these eyes there was complete retinal detachment and advanced degenerative changes, but the central retinal tumour had the structure of a capillary naevus, the matrix of which contained many scattered cells apparently endothelial in character. Cystic spaces abounded in the tumour and in the retina generally, and Collins described the condition as a capillary naevus of the retina with cystic degeneration.

v. Hippel discussed the condition in 1895 from the clinical, and in 1911 from the pathological aspect, and earned for it the name of von Hippel's disease. Coats (1908) described the disease among the forms of retinal disease with massive exudate, and supported the view of Collins, v. Hippel and Czermak that it must be considered as a true vascular new-formation. Lindau (1926) established the close association of v. Hippel's disease with the haemangiomatous cysts of the cerebellum and other organs described by himself. In the subsequent literature on the pathology of v. Hippel's disease emphasis has been placed on the presence of endothelial cells throughout the retinal tumour.

Two views are expressed regarding the pathogenesis of the condition, namely; (1) that the growth is primarily a gliosis which undergoes a secondary vascularisation, and (2) that the vessel formation is primary and the gliosis a secondary reaction. Meller and Marburg (1928) and others who support the first view point out that the glial formation is out of all proportion to the vessels, which may be very scanty. They have also found a massive gliosis without any vascularisation or endothelial cells.

They emphasise that glial masses may be found in the deeper non-vascular layers of the retina: but we are bound to admit that there may be not only persistence and proliferation, but also displacement, of the embryonic cells of origin. One argument in favour of the primarily vascular nature of the growth is that the vessels in the tumour nodules appear to be independent of the local circulation, and have no resemblance to the vascular pattern of the retina. Again Lindau (1936), Paton (1929) and others have examined cases in which the tumour contained no glial tissue, and clinically the vascular aspect of the tumour may be evident for some time before gliosis appears.

The occurrence, in the present case, of clusters of endothelial cells without vessels is significant, and supports the view that the lesion is a haemangio-endothelioma or haemangio-blastoma. The ophthalmoscopic and microscopic features of the case bring it into line with the cases of Lindau (1927), Paton, Williamson-Noble and Greenfield (1929), Sladden (1930) and A. E. Macdonald (1948), which are among the few cases in which the complete v. Hippel-Lindau complex was present and both microscopic and ophthalmoscopic examinations were obtained. The feature common to all these cases is that the actual tumour is composed largely of endothelial cells, some of which proceed to form rudimentary blood vessels. The relative abundance of endothelial cells, blood vessels and glial tissue varies from case to case and even in different parts of the same retina.

From the findings in the present case, it would seem that the initial pathological unit is a cluster of endothelial cells destined to form a vascular endothelium, but persisting in a more or less embryonic state, proliferating and invading the avascular layers of the retina. The overgrowth of neuroglia, the formation of retinal cysts, the widespread hyaline change and the general disorganisation of the retina must be looked upon as secondary. It is evident that the vessels of the angioma are not formed by budding from mature retinal vessels but by the pursuit, by the endothelial cells, of their destined function of vessel-formation. The tumour shows no signs of malignancy, but the eye may be destroyed by the occurrence of haemorrhage, glaucoma or detachment of the retina.

Summary and conclusion

The case is described of a young man who suffered from angiomatosis retinae (v. Hippel) accompanied by cerebellar haemangioma (Lindau). The affected eye was excised and subsequently the cerebellar tumour was removed. Both were subjected to microscopic examination.

The cerebellar tumour consisted of a soft fibro-cellular mass, containing many clear endothelial-lined spaces, some cystic, others vascular. Unorganised endothelial cells were diffused through the matrix of the tumour.

In the retina, which was grossly disorganised, there were

(1) Clusters of endothelial cells, some of the latter grouping themselves to form capillary vessels. The endothelial cell cluster seems to be the pathological unit.

(2) Larger clusters or nodules, some of them filling the whole thickness of the retina, and consisting of a fibro-cellular (glial) matrix containing new vessels of varying size as well as unorganised endothelium.

(3) A hyaline change, first of all at the centre of the nodules, but later converting the whole nodule to a hyaline mass.

(4) Similar changes in a more diffuse form, predominantly a gliosis.

(5) Cystic, pigmentary and other forms of degeneration.

The findings support the view that the vessel-formation is primary and the gliosis of the retina secondary.

The tumour cells are not derived from the large mature retinal vessels. It is probable that they are derived from the capillary endothelium, or rather from the anlage of such endothelium. Such an anlage develops by budding from the vascular endothelium confined at an early embryonic stage to the optic nerve region, and does not develop from neural cells.

The tumour is a true haemangio-blastoma or haemangio-endothelioma.

We would express our thanks to Prof. A. J. Ballantyne for his close interest in this case and his help in working-out the histology.

Fig. 1 is from a coloured drawing of the fundus by Mr. Gabriel Donald.

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ANTIHISTAMINES IN OPHTHALMOLOGY*

BY

LEWIS NÉMETH

HISTAMINE plays an important rôle in the mechanism of allergy or hypersensitive diseases of the constitution. This substance is to be found preformed as histidin in the cells; by the antigen-antibody reaction which acts on the cell-walls, histamine is released and thereafter produces the allergic symptoms. This classically simple interpretation of the allergic process was renewed lately in a more complicated and theoretically preferable form. Several authors believe the allergic reaction to be the result of allergen activating the preformed reagin contained in the cells, and this as catalyser releases a great quantity of H. substance. These H. substances, of which histamine is the most important, produce the symptoms which can be observed clinically. These H. substances which produce the allergic symptoms are products of the irritation of the cells caused by the allergen reaction which starts those well-known changes in the small veins — namely, increase in diameter and permeability.

This short sketch of the allergic mechanism shows the need for variability in the treatment of allergic diseases. Anti-allergic treatment can be specific when we try to prevent the real cause, the meeting of allergen-reagin, by preventing access of the specific allergen to the system. In other cases we try to exclude the reagin by desensitization. This specific treatment is rather complicated, and demands special technique. Therefore simpler methods have been sought in the treatment of allergic diseases, including those of ocular origin. Such were found when the significance of the H. substances in the causation of allergic diseases became known, and it seemed desirable to eliminate these H. substances. Such treatment was not specific, and had formerly been tried in utilising the fermentation of histamine to alleviate allergic diseases. Long ago we used "Torantil" for this purpose. This proteid substance, derived from the mucuous membrane of the intestines, can inactivate histamine and sometimes restrains allergic manifestations. One tablet was prescribed three times daily, but it often fails in practice notwithstanding its theoretical value.

The difficulty of searching for a specific antigen and the technical obstacles to be overcome before it can act as a desensitiser induced me some years ago to use histamine to lessen or abolish constitutional hypersensitivity. The diagnostic value of the histamine

* Received for publication March 1, 1949.

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skin-test which I formerly recommended was also an aid in deciding the line of treatment. When the histamine skin-test was positive, I tried to lessen hypersensitivity in allergic eye-diseases by injecting histamine under the skin. I noted obvious and lasting results several times, and this treatment is often used by us in allergic eye-diseases. It is uncertain how histamine hypodermically administered in small, increasing doses, produces a favourable result in allergic eye-diseases. Perhaps increasing doses of histamine accustom the constitution to endogenous histamine effects, such as may arise in an allergic disease. The beneficial effect of histamine introduced in increasing quantities is based not so much on the production of antibodies, as on the outpouring of adrenalin thereby provoked. Histamine can produce the formation of antibodies only in the form of complex antigen, so that presumably the good effect of histamine treatment is due to adrenalin, though histamine subcutaneously linked with tissue-protein plays the part of a complex antigen.

Recent researches have produced synthetic substances which can inhibit histamine. Amidst the numerous experimentally tested drugs are several so-called anti-allergic drugs used clinically with success. The basis of the knowledge is the protective effect of certain phenol-ethers against histamine intoxication. Staub and Bovet in 1937, stated that fatal anaphylactic shock of a hypersensitised guinea-pig can be avoided by thymoxyethyldiæthylamin 929 F, but this substance proved toxic. Further research resulted in such synthetic anti-histamines as antergan, neo-antergan, antistin, benadryl and pyri-benzamin. All of them neutralise histamine, abolish or minimise allergic manifestations and are almost non-toxic. Antergan medicinally used in France has caused death, but neo-antergan is less toxic. The daily dose of each is 0.6 gm., benadryl and pyridenzamin are produced in America, and the dose of each is 50 mgm. by the mouth. Favourable results were obtained in allergic diseases such as urticaria, œdema of Quincke, hay-fever, vasomotor rhinitis and pruritus. Dean recently described a case in which fever due to penicillin treatment, dyspnœa and general urticaria ceased a few hours after administering 130 mgm. of benadryl. Its accessory effects, such as fainting, palpitation and nervousness, are mild.

Rosso considers ocular manifestations in the intermenstrual period of certain women as allergic. He believes that in this period there is a surplus of histamine-like substances. These disturb the biochemical equilibrium of the aqueous humour and conduce to various eye diseases. Hence we cannot always obtain good results from hormonal treatment. On this basis Rosso tried to utilise dimethyl-amino-ethyl-benzylamidin-hydrochloride, the antagonist of histamine

as an anti-histamine substance. Intermenstrual episcleritis and uveitis reacted well so did conjunctival, eye-lid and other manifestations. He administered the drug orally, intravenously in a 2·0 per cent. solution, and as drops in 0·5 per cent. solution. We have no personal experience of these drugs.

The Ciba factory kindly allowed us to test their antihistamine product antistin, and we found it effective. It is a derivative of imidazolin of the priscol-privin series. Meier and Bucher verified by animal experiments in 1946 its antagonistic action upon histamine. It is uncertain whether this action is direct desensitisation of histamine or whether it can be otherwise explained, but at any rate we can expect results from antistin treatment when organic changes in the allergic constitution have not yet developed. Its favourable effect can be observed in anaphylactic symptoms and allergic diseases, as well as in diseases caused by allergic-inflammatory factors, *e.g.*, nephritis. This effect was also described in the Hungarian literature for internal medicine. This drug was employed in many different diseases with striking success. It can be used in tablets of 100 mgm. orally, or by intramuscular injection. The average daily dose is 300 mgm. but more can be given without provoking toxic effects. Ophthalmologists are especially interested in the solution which can be applied as drops. The watery solution contains 0·5 per cent. antistin and 0·025 per cent. privin. Privin, being an imidazolin derivative checks swelling of the mucous membrane, and by contracting the veins even more than does adrenalin, it potentiates the antistin effect. We observed the remonstrable effect of antistin-privin drops in many different allergic eye-diseases, as in the following case.

1. H. G., a 60-year-old man, complained that his right upper eye-lid swelled suddenly and became irritable though not painful. His right eye was watery. On the previous night he had eaten eggs. On the right upper eye-lid there was a typical oedema of Quincke, and on the same side allergic conjunctivitis. After half-an-haur poulticing with a tampon soaked in antistin-privin solution, together with instillation of drops, he went away cured. It was not possible to determine the aetiology. Histamine skin-test was positive.

2. Sz. K., a 35-year-old man, gave a history of eczema on the scrotum and both legs in 1942. In Spring, 1943, eczema appeared on the right ear. He was treated with his own blood-serum, autovaccination from his tonsils, Castellani solution. A week ago his right eye became inflamed, and he was elsewhere given noviform ointment and targesin solution to use at home. On examination his right eye-lids were greatly swollen by involvement in the moist eczema. The inflamed conjunctiva showed increased sensitivity, as corroborated by the presence of eosinophil cells in the conjunctival sac. The histamine skin-test was strongly positive. After three days of treatment with antistin instillation and antistin tablets three times daily by mouth, the skin of the pale eye-lids peeled in scales, the conjunctiva whitened, and secretion ceased. Those who have treated such eye-diseases know, that, with ordinary therapeutic measures, resolution takes 8-10 days.

3. R. H., male, 65 years, had been treated as an out-patient for 11 months for subacute allergic conjunctivitis. It was not possible to discover the origin of the malady but he said it developed after heavy sweating from strenous physical work. In spring he usually had a cold. The blood picture was normal, and the histamine-test positive. Before the administration of antistin he had been unsuccessfully

treated with various drugs. His discomfort ceased after a week's instillation with antistin once daily. In 10 days he completely recovered, and there have been no relapses in the past six months.

4. Cs. L., a 40 year-old woman, had been treated for similar trouble in her right eye at an insurance hospital for six months. Various drops and milk-injections afforded no benefit. She stated that she was cured by penicillin ointment in another hospital, but three months after her recovery fresh inflammation arose in her right eye. She showed marked photophobia, and there were 8-10 superficial punctate infiltrations scattered over the cornea. This superficial keratitis, of which the cause was obscure, was probably a form of hypersensitivity, and it cleared after instillation of antistin once daily for three days. The histamine skin-test was strongly positive in this case also.

We have observed rapid benefit from antistin treatment in cases of blepharitis due to penicillin hypersensitivity, and in conjunctival diseases. The prolonged use of sulphonamides and antibiotics can sensitize the organism. Allergic symptoms arising from such causes are favourably influenced by antistin.

The same benefit ensued in a man with conjunctivitis accompanying widespread dermatitis provoked by a mercury skin ointment applied once only. Antistin instilled once daily for 3-4 days relieved him of his eye-symptoms, and also abolished eye-symptoms due to sensitization by pilocarpin.

We also observed beneficial results in the conjunctivits of hay fever. The patient rapidly lost his discomfort. Success was also obtained in spring-catarrh treated with antistin, orally or in drops. Symptoms ceased or were relieved, though the objective picture scarcely changed.

Györffy and Kahán tried antistin in patients complaining of irritation from the wearing of contact-glasses. They supposed that over sensitiveness to the contact-glass, irritating the cornea, produced in some people an increase of histamine. More than half of these patients could wear the contact glass for a longer time after previous instillation of antistin, than they could without antistin.

Subsequently we saw favourable results in the oedema of Quincke, acute and subacute conjunctivitis accompanied by allergic dermatitis, eczema, allergic conjunctivitis including that of hay-fever, spring-catarrh and superficial keratitis. Antistin given orally checked the reactions of hypersensitivity caused by penicillin,

Finally, we must mention episcleritis, iridocyclitis and uveitis of focal origin. It is supposed that noxious foci produce antigens, which cause allergic outbursts, *e.g.*, iridocyclitis, by sensitizing the constitution. The ideal solution would be to stop the production of antigen by removal of the focus. Belated removal of the focus does not, however, always prove beneficial owing to an increase of parallergy. This explains frequent relapses even after removal of the focus. In such cases peroral treatment by antistin seems theoretically sound, but success in a few cases does not permit far-reaching assumptions, and further investigations are required. Bourquin relates similar observations. With this same object we used the 5497/3 nr. anti-allergicum produced by the Hoffmann-la Roche factory. This drug is available in America under the name

of Tephorin. We used it successfully for cases of chronic uveitis, in which moderate increase of monocytes denoted hypersensitivity. Good results were also obtained in some cases of spring-catarrh, though one patient complained of insomnia. He was taking 3-6 tablets a day.

In conclusion we can assert that the discovery of synthetic antihistamine substances offer a new method of treatment for allergic diseases. Such treatment is at once palliative and symptomatic. These histaminolytic substances are beneficial in ocular disease, and our results with antistin encourage us to advise these substances for trial.

Summary

The mechanism of allergy and various forms of allergic treatment are reviewed. Specific treatment is not always possible. The knowledge of H. substances opens up new methods of treatment. The notion of rendering substances such as histamime ineffective has been under consideration. One may try to accustom the constitution to histamine or to desensitise the organism thereto. For diagnostic purposes in eye diseases, I advise the histamine skin-test, and note the good results obtained in allergic eye diseases by small subcutaneous injections of histamine. The latest anti-histamine drugs can inhibit histamine, and combat allergic eye diseases. Experience with antistin produced by Ciba are reviewed. Good results were seen in the oedema of Quincke, acute and subacute conjunctivitis associated with allergic dermatitis, eczema, allergic conjunctivitis, hay-fever, spring-catarrh and superficial keratitis. Antistin favourably influenced the hypersensitivity reactions caused by penicillin. In all these conditions it was applied locally, but in the treatment of episcleritis and uveitis of focal origin antistin given by the mouth often proved beneficial. In view of the good results obtained these antihistamine substances can be recommended for trial by ophthalmologists.

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SOME WAR TIME STATISTICS*

BY

G. C. DANSEY-BROWNING

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THE recent publication of a Statistical Report on the Health of the Army from 1943 to 1945[1] has provided the military ophthalmologist with a wealth of information. This work presents some of the ophthalmic problems peculiar to troops stationed in the United Kingdom, and outlines some of those encountered during the campaigns of Europe and Africa. At first sight such statistics would appear to have only a limited value in this atomic age, but it must be remembered that the basic morbidity rates for ophthalmic disease amongst British soldiers will remain virtually unaltered in all future wars. Atom bombs, on the other hand, will affect the casualty rates considerably, and may even align the figures for ophthalmic injury in the 1939-1945 war with those of campaigns of a bow-and-arrow era.

European armies by 1939 had achieved only relatively slight increase in efficacy of the explosives and projectiles used, compared with those employed in the wars of the previous half-century. Thus the histories of these conflicts gave the military oculist some rule-of-thumb data to go by. Some two-and-a-half per cent. of the total battle casualties would thus be expected to have sustained wounds of the eye and orbit. If, however, wounds of the head and neck region were aggregated, these might even prove responsible for up to ten per cent. of the injured that were evacuated from the battle-field. The ophthalmologist expected, and indeed soon learned by his own experience that, if a soldier were to be hospitalised for any ophthalmic lesion, then that man's unit would be lucky if it received him back under a month. It would be suspected that ophthalmic disease was only responsible for about one per cent. of the total sickness amongst British troops in most parts of the world, and the ophthalmologist would find that about five per cent. of the personnel of a fighting division and from ten to fifteen per cent. of personnel of the L. of C. troops would need spectacles to render them militarily efficient. It is interesting to compare these pre-conceptions with the figures for disease and injury given by statisticians.

OPHTHALMIC MORBIDITY IN THE UNITED KINGDOM

The report provides us with the startling generalisation that the overall sickness rate in the United Kingdom during 1943 was such

* Date submitted for publication, May 27, 1949

that every soldier might well have spent one day of that year in reception stations, and eleven days in hospital or convalescent depots. It is interesting to note that two-thirds of all the military cases of ophthalmic disease were treated in the Army's own hospitals, while the other third were treated in civilian hospitals under the Emergency Medical Scheme. Cases suffering from eye disease in 1943 comprised some two per cent. of the population of military hospitals.

The relative casualty rate — that is, the percentage of eye disease amongst all persons lying in hospitals either for reason of sickness or injury — proved to be 1·4 for all male other ranks and 0·8 for members of the Army women's services (A.T.S.). On exclusion of the persons in hospital because of injury, we obtain the relative morbidity rate for ophthalmic disease, and this worked out as 1·0 per cent. for the male other ranks, and remained, as might be expected, at 0·8 per cent. for the A.T.S. The mean duration of stay in hospital for cases of eye disease was found to average out as 28·4 days for male other ranks and 24·3 days for the A.T.S.

OPHTHALMIC MORBIDITY IN THE MIDDLE EAST

Since the days of the Bible the history of war in the Middle East has abounded with descriptions of epidemics of the ophthalmias amongst the armies engaged. The following figures are therefore particularly instructive: The relative casualty rate in 1943 amongst hospitalised other ranks was 1·87 per cent. for ophthalmic lesions. This was therefore only an increase of approximately a third above those hospitalised in the United Kingdom. The relative casualty rate for the officer hospital population proved only to be 0·72 per cent.

Further analysis in the report showed that conjunctivitis accounted for 0·74 per cent. in 1943 and 0·73 per cent. in 1944 of all lesions amongst the other rank hospital population. The diagnosis of keratitis in 1943 covered 0·50 per cent. of all lesions and in 1944 some 0·49 per cent. The officer hospital population suffered far less from conjunctivitis or keratitis. Thus the conjunctivitis incidence in 1943 amongst officers was 0·29 per cent. of the total lesions and keratitis 0·25 per cent. In 1944 the morbidity rate was 0·25 per cent. for conjunctivitis and 0·19 per cent. for keratitis.

The Middle East ceased to be the theatre of large scale operations in the autumn of 1943, and the consequent lessening of urgency in the need to return men to the front is reflected in the increased time that eye cases now spent in hospital. The average time in hospital for the conjunctivitis cases rose from 18·6 days in 1943 to 22·5 days in 1944, and for the keratitis cases from 27·9 days in 1943 to 32·9 days in 1944. The Middle East Force at this time was a polygot army,

and some interest lies in the variety in the incidence of ophthalmic lesions amongst troops of different races. The relative casualty rate for United Kingdom troops with ophthalmic disease in hospital worked out at 1·6 per cent. for Dominion troops at 1·8 per cent. for British African troops at 1·7 per cent. whilst for Indian troops it was 5·6 per cent. That the Indian troops were thus badly affected was probably due to the fact that since 1930 recruiting regulations had been relaxed to permit of the enlistment of men with "healed trachoma." The incidence of trachoma amongst Indian troops is held by some authorities to be almost one hundred per cent.

SEASONAL INCIDENCE OF CONJUNCTIVITIS AND KERATITIS IN THE MIDDLE EAST

This portion of the earth's surface is regularly plagued at certain times of the year with heat, dust and flies. The two graphs show that the highest incidence of conjuntivitis and keratitis do not directly coincide with the main "Khamseen" and fly-breeding

ONE HUNDRED CASES OF CONJUNCTIVITIS

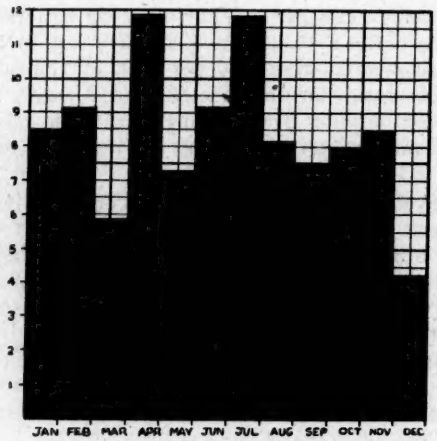

FIG. 1.

periods. Among the various units the R.A.O.C. suffered most from conjunctivitis. This was to be expected from the nature of their duties, of necessity carried out with little protection from the elements in large sandy Ordnance Depots.

ONE HUNDRED CASES OF KERATITIS

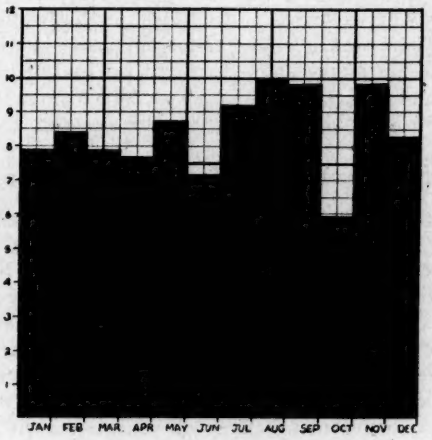

FIG. 2.

OPHTHALMIC MORBIDITY IN THE CENTRAL MEDITERRANEAN FORCE

The report divides the ophthalmic lesions incurred in this theatre of war into 49·9 per cent. conjunctivitis, 25·5 per cent. keratitis, and other ophthalmic disease 24·6 per cent. The relative casualty rate in 1944 was worked out at 1·1 per cent. for other ranks, and 0·4 per cent. for officers. During the whole period under review the C.M. Force was engaged in active operations against the enemy in Italy. The mean duration of stay in hospital proved to be 22·4 days, ranging from an average of 18.7 days for the conjunctivitis cases to 30·1 days for those of keratitis.

DISCHARGES FROM THE ARMY

Men suffering from intractable ophthalmic lesions or with vision below the requisite standards for service were generally made to take their discharge from the Army in the United Kingdom. Thus during 1943 cases of eye diseases constituted some 2·2 per cent. of the total discharges from the Army for sickness or for injury. In 1944 this percentage had fallen to 1·55 per cent., and again in 1945 to 1·15 per cent. Corresponding figures for the A.T.S. worked out at 1·4 per cent. in 1943, 0·9 per cent. in 1944 and 0·7 per cent. in 1945. Thus the effects of lowering the minimal visual standards in the last years of the war are reflected in the change in these

figures. From another standpoint it can be said that, for every 100,000 male other ranks in the Army in 1943, some 48·3 had to be discharged for "eye-disease." In 1944 this had fallen to 39·4 per 100,000, but there was a slight rise again in 1945 to 40·6 men per 100,000 due to shrinkage of the army at the end of hostilities. An equal strength of A.T.S. would have lost 28·6 women in 1943, falling to 18·6 in 1944 and showing a very minor increase to 18·7 in 1945.

INVALIDING DISABILITIES AMONGST PRISONERS OF WAR

The recording of invaliding disabilities amongst prisoners of war, and especially those returned from the Far East, showed up one real difficulty in the application of statistical methods to medicine. The problem lies in the separation of the so-called primary and secondary invaliding disabilities. For example a P/W from the Far East had often contracted malaria, dysentery, beri-beri and an "optic neuritis." The invaliding medical officer would therefore have some difficulty in recording what constituted the "primary" disabilities, when his examination took place some years after the onset of these several diseases. Thus the allocation of the primary disability often became merely an expression of the medical officer's personal opinion derived from a vague clinical history.

In the statistical report the term "optical neuritis" was made to include retro-bulbar neuritis and optic atrophy. Other ophthalmic evidence of nutritional amblyopia was duly recorded as "defects of the field of vision." So the recorded primary disabilities amongst Far Eastern Ps./W. gave some 5½ per cent. as having incurred optic neuritis and a further 2 per cent. as showing defects of the field of vision. As soon as the secondary disabilities were taken into account, then the percentage of those discharged with either optic neuritis or defects of the field of vision rose to 11 per cent. of the total. There is an interesting comment that, at the time of their discharge from the Army, 25 per cent. of the men still showed effects of nutritional deficiency.

The following table gives an excellent comparison of the discharge rates for primary disabilities of the eyes.

Diagnosis	*Non-Prisoners*	*P.s/W. Europe*	*P.s/W. Far East*
Defects of the Field of Vision	0·3 per cent.	0·2 per cent.	2·0 per cent.
Optic Neuritis	0·1 per cent.	0·1 per cent.	5·6 per cent.

OPHTHALMIC BATTLE-CASUALTIES AND BATTLE-ACCIDENTS

The term battle-casualties is in common usage, but the term battle-accident may require some elaboration. It is employed to categorise the men who are indirectly injured by the enemy. Thus

the man may have sprung a booby-trap laid by the enemy some months before; or, for example, by the faulty handling of his own weapons in the field, the soldier may have detonated his own hand-grenades, although not in the presence of the enemy. "Battle-accident" therefore covers most of the accidents which might happen to the soldier as he carries out his calling in the field, except those caused by wilful negligence.

The report includes interesting statistics mainly obtained from the records of the North African campaigns. In that fighting, the rôle of the specialist surgical units in the field was such that, from their returns, it was possible to make a classification of wounds on an approximately anatomical basis of sites of injury. In the Normandy landings, a regional classification for wounds came into use in the place of the Neuro-surgical, Facio-Maxillary, Ophthalmic, etc., method used in the earlier campaigns. This regional method is probably the most logical way to record casualties, because wounds are often multiple, and their distribution often crosses the anatomical lines of demarcation, but, as will be seen later, figures obtained from casualties suffering from wounds of the head and neck region are unsatisfactory when the types of wounds of the eye have to be discussed.

The North African casualties were analysed for three separate two-month periods of intensive battle-fighting as under:—

Battle	*Period*	*Army Engaged*
Knightsbridge	May-June, 1942	VIII Army
El Alamein II	Oct.-Nov., 1942	VIII Army
Tunisia	Dec., 1942-Jan., 1943	I Army

In the three battle-periods above, wounds of the head, face or eyes were responsible for 12-17 per cent. of the total casualties.

Battle	*Neuro-surgical cases*	*Facio-Maxillary cases*	*Ophthalmic cases*
Knightsbridge	5·3 per cent.	4·3 per cent.	2·2 per cent.
El Alamein II	4·9 per cent.	7·0 per cent.	2·7 per cent.
Tunisia	9·5 per cent.	5·5 per cent.	1·6 per cent.

There were many casualties during all these three periods not strictly due to direct enemy action, *i.e.*, as later described, "battle-accidents." Thus some fifty per cent. of the Knightsbridge cases were battle-accidents forty-five per cent. at El Alamein II, and forty-eight per cent. in Tunisia.

When the casualties from the June-July Normandy landings in

1944 were analysed, the report states that only 15 per cent. of the campaign injuries were held not to be due to direct enemy action. Considering that a large proportion of the troops in the spearhead of the attack were the same men who had participated in the Middle East campaigns, it would seem that this point merely emphasizes the more generous method of recording a man's injuries.

The fighting troops in the North African campaigns were generally carried into battle in armoured or unarmoured petrol-driven vehicles. When hit in a vital part these vehicles would "brew-up," as the current expression described it. Therefore among the ophthalmic casualties there would be a large number of burns of the globe and adnexa. Among the total ophthalmic casualties at the Knightsbridge battle there were 5·1 per cent. burns cases, at El Alamein II some 4·8 per cent. and in Tunisia (where there were many tank casualties) some 7·7 per cent.

The report states that a very high proportion of the ophthalmic casualties were eventually returned to duty in the same theatre of operations. Thus from the Knightsbridge battle some 79·7 per cent. from El Alamein II some 77 per cent. and from the Tunisia fighting 66·7 per cent. were returned to duty in North Africa. Such figures, however, must be treated with caution, as they do not give any indication of the man's final visual efficiency, nor of the employments for which he was finally fit. For example, most of the North African theatre oculists will agree that very few infantrymen who had sustained a penetrating wound of the globe were ever fit for front-line service again, although they might be employable at the base, or on the lines of communication.

The report also makes mention of the remarkable consistency in distribution of the wounds of different parts of the body in all four campaigns. In Normandy some twelve per cent. of the total casualties were found to have suffered from wounds of the head and neck region. Of these, some 13·7 per cent. were ***lethal***, death occurring during evacuation through medical units; 21·6 per cent. were ***severe***, and prolonged hospitalisation of the men resulted; 42·3 per cent. were ***medium***, and in these cases only short hospitalisation was necessary; 22·4 per cent. were ***trivial***, so that, after treatment in the forward medical units, the men were returned to their units.

Single as opposed to multiple wounds of the head and neck region were grouped in the report as superficial 10·4 per cent.; flesh 70·9 per cent.; bone 12·6 per cent.; and burns 3·3 per cent., while concussion was only 2·7 per cent. This emphatically did not tally with the experience of most ophthalmologists, who accepted that eye-wounds due to blast as opposed to those from direct trauma by a projectile might form up to forty per cent. of the injuries of the

globe. Here is an instance in which the regional method of wound classification has its limitations.

It was interesting to read that the infantry sustained up to 80 per cent. of the mortar wounds but only some 50 per cent. of the mine wounds. The supporting troops were affected most by mine or bomb wounds, and it was also notable that half the wounded artillery men had been injured by the enemy's counter-battery fire.

SPECTACLES AND THE SOLDIER

As long ago as 1915, when the general introduction of spectacles into the Army was being carried out, it was estimated that five per cent. of every fighting division would need spectacles to make them militarily effective. This estimate was found valuable in the recent war. Some American statistics in respect of their draft (recruits) published in 1944 showed that 5·5 per cent. of the men enlisted had vision in the one eye of 6/18 or less[2]. A survey of British recruits in 1946/1947 gave a figure of 8·8 per cent. of the recruit intake as having vision of 6/18 or less in one eye[3]. Recently when recruits for the line of communication troops were examined, out of some eight thousand men some fifteen per cent. were found to need glasses. These would be men of slightly lower physical capacity than the fighting troops in a division. Under the Pulheems system of classification, wherein ophthalmic lesions give alteration of the P. rating (Physique), some 5 per cent. of these men were below P.2 (the normal). 298 men were placed in the P.3 rating, which is the "strabismus" rating.

Summary

(1) The figures for ophthalmic injury and disease quoted in the Statistical Report on the Health of the Army, 1943-45, agree in the main with the expectations of military ophthalmologists.

(2) The ophthalmic morbidity amongst the soldier population at home and abroad will not markedly alter in future wars, and it is to be hoped that statistics of this nature will not have been forgotten by the time of the next conflict.

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THE EFFECT OF HYALURONIDASE INJECTION ON THE VITREOUS HUMOUR OF THE RABBIT*

BY

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THE effect of hyaluronidase injections on the slit-lamp appearance and the composition of the vitreous humour of the rabbit has been examined. The purpose of the experiments has been to see whether disaggregation of hyaluronic acid from a viscous to a non-viscous form in the vitreous humour is a permanent change and whether any visible change persists as a result of hyaluronidase action. Very little is known of the production or fate of hyaluronic acid, either in the eye or in other fluids and tissues of the body, such as synovial fluid, skin, or Wharton's jelly, where it also occurs. Meyer (1947) has suggested that there is a circulation of hyaluronic acid in the eye, the viscous hyaluronic acid of the vitreous humour being disaggregated and removed through the normal exit channels. Presumably this is a very slow process in the normal eye and we do not know whether complete disaggregation of the vitreous hyaluronic acid, such as might take place under pathological conditions, can ever be reversed. Nor has any clinical change been correlated with such breakdown. Aggregated hyaluronic acid is the viscous material that contributes to the turgor of the vitreous humour and its loss—if irreversible—might possibly lead to considerable changes in the state of the vitreous body.

von Sallmann (1948) has briefly described the effect of injections of hyaluronidase on the vitreous humour of the rabbit. He found that the enzyme caused a considerable inflammatory response and considered its use too dangerous for clinical purposes. In the experiments reported here the eyes have been watched for nearly a year after injection of hyaluronidase to see if permanent change occurred and the vitreous humours have been analysed to see whether the chemical changes could be correlated with any clinical change. The eyes were examined with the slit-lamp and ophthalmoscope, and the composition of the vitreous humour, sometimes also of the aqueous humour, was determined when the animal was killed. In a few animals the effect of hyaluronidase on intra-ocular pressure was noted. The state of aggregation of hyaluronic acid was judged by the type of mucin

* Received for publication, January 6, 1949.

clot it gave in acid acetone. The enzyme system hyaluronidase causes a rapid disaggregation followed by a slow hydrolysis of hyaluronic acid. The primary change only has been studied, as this seemed the most important relative to vitreous humour structure. Disaggregation can be followed either by following the change in the type of mucin clot produced by acidification of the vitreous humour filtrate, or in some cases by following the reduction in viscosity of hyaluronic acid due to disaggregation. Although a viscometric method is preferable, it could not be used here as increase in protein in the vitreous humour raised the viscosity and this overshadowed any possible fall due to change in hyaluronic acid.

The total nitrogen content of the vitreous and aqueous humours was determined to give a picture of protein movement in the eye and the hexosamine content was determined in the hope that it would reflect changes in the hyaluronic acid of the vitreous humour. The change in protein—which contains small amounts of hexosamine—was however so large that hexosamine change reflected only this.

In all these experiments one eye of each animal was injected with active enzyme and the other with an equal volume of the enzyme solution after inactivation by boiling.

METHODS

Total nitrogen was estimated by micro-Kjeldahl followed by distillation and titration, using the apparatus described by Markham (1942).

Hexosamine was estimated by the method of Elson and Morgan (1933) modified for use with small volumes. 0·5 ml. or less of vitreous humour filtrate or 0·1-0·2 ml. aqueous humour were used. The samples were put in small glass bulbs of about 3 ml. capacity and having a wide neck of about four inches long. The hydrolysis, acetylation and reaction with Ehrlich's reagent were all done in these bulbs without transfer and the final volume was brought to 3 ml. Colour was estimated by a Hilger Biochem absorptiometer, using Filter No. OG.1 (Hilger). A reagent blank and glucosamine standards were carried through all stages with each estimation.

State of aggregation of hyaluronic acid. The state of aggregation of hyaluronic acid was estimated by observing whether a fibrous or flocculent precipitate was given when the filtrate of the vitreous humour was added to acid acetone (Robertson, Ropes and Bauer, 1940; Pirie, 1949).

Preparation of hyaluronidase. The enzyme was prepared from rabbit testis by the method described by Madinaveitia (1941). The preparation was taken as far as the precipitation with NaCl and then dialysed against 0·9 per cent. NaCl. The dialysed solution was sterilised by filtration through a collodion membrane of a.p.d. 0·82μ.

Test of hyaluronidase activity. The disaggregating effect of the enzyme on the hyaluronic acid of the ox vitreous filtrate was used as a test of enzyme activity. Two ml. ox vitreous filtrate were mixed with 0·1 ml. enzyme at 30°. Samples were precipitated at intervals in 3 vol. acid acetone and the time taken for the enzyme to change the character of the precipitate from a compact fibrous one to a cloud-like precipitate was taken as an indication of the activity of the enzyme.

Method of injection of enzyme into vitreous humour. Dutch rabbits of either

sex and between four months and one year in age were used. The animals were anaesthetised with intravenous nembutal and the eyes were cocainised. The enzyme or boiled enzyme solution was injected a little behind the equator, care being taken to avoid the lens, which is large in the rabbit. A 26 gauge (American) needle on a 0·25 ml. syringe was used for injection. Enzyme solutions containing 0·15-0·25 mg. protein/ml. were used.

Preparation of aqueous humour and vitreous humour for analysis. In some experiments aqueous humour was removed from the animal during life. The animal was anaesthetised and aqueous humour removed by inserting a small glass capillary pipette through the cornea. About 0·2 ml. fluid ran into the pipette without suction.

At the end of the experiment the rabbit was killed either by a blow or with nembutal. The eyes were removed, carefully cleaned of all external tissue, rinsed in saline and then dried. The aqueous humour was then removed, the eyes dissected equatorially and the vitreous humour pulled away from the retina. The anterior half of the eye, together with the attached vitreous humour, was then put on a small glass mesh filter and allowed to drip into a centrifuge tube in the ice chest. Filtration usually took about ½-1 hour. The filtrate was then centrifuged to remove pigment and cells and the clear supernatant fluid analysed.

RESULTS

Reaction of Vitreous Humour to Injection.—Injection of the active enzyme preparation caused a prolonged inflammatory reaction in the eye. This reaction also occurred after injection of the heated enzyme, or of saline, but was usually much less severe. I found that the reaction to the heated enzyme—a reaction that is presumably unspecific in nature, due to trauma or introduction of foreign protein—could be reduced if the volume of injected fluid were kept as small as possible. If 0·1 ml. of heated enzyme diluted 1/5 with saline were injected, the reaction of the eye was worse than to 0·02 ml. undiluted enzyme. Injection of 0·1 ml. into a rabbit's vitreous humour raises the tension to over 100 mm. Hg on the Maclean tonometer for a few minutes and it may be this sudden rise of tension that is responsible for the inflammatory response. The rise after 0·02 ml. injection is not noticeable.

Reaction to Active Enzyme.—Within two hours after injection, either of 0·02 ml. or 0·1 ml. enzyme preparation, the aqueous humour showed a marked flare. The fundus and vitreous humour appeared normal both to ophthalmoscopic and slit-lamp examination. After 24 hours the aqueous humour contained many circulating cells and a dense flare. The fundus was usually quite normal, but the central area of the vitreous humour was hazy. In three days the aqueous humour still showed a flare, but the number of cells was diminishing. The vitreous humour was usually full of brightly refractile particles, probably cells, sometimes attached in clumps to the back surface of the lens and scattered throughout the visible anterior part of the humour. The retina usually appeared normal, but in a few cases patches of

exudate appeared in the lower part of the fundus. From this time the anterior chamber gradually cleared and was usually normal in from six to fourteen days. The vitreous humour cleared more slowly and reached a steady state in about a month's time, when there would be a few cells visible. The normal rabbit's vitreous humour shows very little in the slit-lamp beam. The humours of the injected rabbits did not return to this optically empty state, but showed a few refracting streaks running usually vertically or at an angle of 45°. The vitreous humour did not appear grossly changed in any case.

Reaction to Heated Enzyme.—Injection of 0·02 ml. heated enzyme into the vitreous humour caused no reaction in the aqueous humour. Injection of 0·1 ml. enzyme diluted 1/5 caused in general a reaction similar to, but milder than, that caused by the active preparation. In two cases the reaction was indistinguishable from that to the active enzyme. The reaction in the vitreous humour was very like that to the active enzyme, both in type and in duration. In fact, it was noticeable that the difference between the two eyes, the one injected with active and the other with inactive enzyme, was more easily seen in the aqueous humour than in the vitreous humour, the site of the injections.

Effect of Hyaluronidase on Aggregation of Hyaluronic Acid.—The state of aggregation of hyaluronic acid was measured by the method described. Even with the small amounts of material available the change in type of precipitate after hyaluronidase action was perfectly clear. The normal vitreous humour, or the vitreous humour injected with heated enzyme, gave a very small fibrous precipitate in a clear supernatant. The vitreous humour injected with active hyaluronidase gave a cloud only, which might settle to a flocculent precipitate after some time. The activity of the enzyme used was such that 0·1 ml. of enzyme diluted 1/5 added to 2·0 ml. ox vitreous humour filtrate disaggregated the hyaluronic acid in it in 30 seconds at 30°.

Earlier experiments have shown (Pirie, 1949) that hyaluronidase acted much more quickly in the filtrate of the ox vitreous humour than in the intact excised eye and this was considered to be due to the restraining influence of the fibrous protein on the diffusion of the enzyme. One can, therefore, expect that an amount of enzyme which will disaggregate hyaluronic acid almost instantaneously in a vitreous humour filtrate may take some hours to act *in vivo*. The shortest time interval investigated was four hours and I found that after this time complete disaggregation had taken place in the living eye. Eyes removed at later intervals after injection showed that the hyaluronic acid of the vitreous

humour remained in the non-viscous disaggregated form for at least a month. Thereafter it seemed to return to normal. The humours that contained disaggregated hyaluronic acid were not liquefied, but were more fragile and filtered much more rapidly than the normal humours. The results showed quite clearly that rabbits killed up to six weeks after injection of hyaluronidase had disaggregated, and rabbits killed six or more weeks after injection had normal aggregated hyaluronic acid in their vitreous humours. In no case did injection of inactivated enzyme have any effect on the state of hyaluronic acid.

Changes in Nitrogen and Hexosamine after Hyaluronidase Injection.—Nitrogen and hexosamine were estimated in both vitreous and aqueous humours when the rabbit was killed. The time of death ranged from 4 hours to 8 months after enzyme injection.

There was a 2—3 fold rise in nitrogen, from 0·27—0·7 mg./ml. in the vitreous humour 24 hours after injection of active hyaluronidase. This was accompanied by a slight rise, from 40—100 μg./ml. in the hexosamine content. The vitreous humour injected with heated enzyme showed similar but slighter changes. Both nitrogen and hexosamine returned to normal about 28 days after injection of active or inactive enzyme.

The changes in the aqueous humour after injection of active enzyme into the vitreous were more pronounced and took place earlier than the changes in the vitreous humour which seems to show that there must be very rapid diffusion between the vitreous and the aqueous humour. Two hours after the injection into the vitreous humour, the aqueous humour nitrogen had risen 10 fold and remained between 3—6 mg./ml. for 24 hours. Hexosamine rose to 500—900 μg./ml. After 24 hours both nitrogen and hexosamine fell and were normal 14 days after the injection. The changes in the aqueous humour of the eye injected with heated enzyme were very much slighter.

The total nitrogen analyses showed that the influx of protein into the aqueous humour is much greater than into the vitreous. This is probably due to the fact that the increase in protein in the vitreous is due to a cell invasion, while soluble proteins derived from capillaries appear in the aqueous humour a short time after injection of active enzyme into the vitreous.

DISCUSSION

The results reported briefly by von Sallmann (1948) showing that injection of hyaluronidase into the vitreous humour causes an inflammatory reaction, have been confirmed. The main point

of interest in the long-term experiments reported in this paper lies in the fact that some time after subsidence of inflammation the vitreous humour hyaluronic acid is again in the viscous, aggregated condition.

The return to normal of the vitreous humour hyaluronic acid probably shows that production of hyaluronic acid is a continuous process in the living eye. Liquefaction of the vitreous humour in man appears to be non-reversible, but judging by experiments with ox vitreous humour reported by Pirie, Schmidt and Waters (1948), liquefaction is more directly related to destruction of the fibrous protein of the humour than to change in hyaluronic acid. Meyer (1947) has already suggested that hyaluronic acid is constantly produced and removed from the eye. The experiments reported here give some proof for this by showing that in the living animal hyaluronic acid is gradually replaced in the viscous aggregated form after it has been hydrolysed by injected hyaluronidase.

The cells which produce hyaluronic acid either in the eye or elsewhere are not known. Hechter (1948) found that, in human skin, the effect of an injection of hyaluronidase on wheal formation (spreading factor effect) is lost after 24—48 hours, showing that in this tissue hyaluronic acid is either re-formed in this time, or diffuses in from surrounding areas. It seems unlikely that diffusion into the vitreous humour from surrounding tissues takes place and easier to consider that hyaluronic acid is re-formed in the eye.

If hyaluronic acid is formed in the tissues surrounding the vitreous humour and secreted in the aggregated form, its diffusion into the humour structure must be very slow. In the ox vitreous humour I found (Pirie, 1949) that hyaluronic acid washed out of the humour very slowly indeed and that it was always found in the disaggregated state in the wash water. The humour of the rabbit contains a lower concentration of hyaluronic acid than that of the ox and is less coherent and firm a structure, so that it is possible that hyaluronic acid diffuses more easily. On the other hand, it is possible that it is produced by the cells that invade the humour after enzyme injection.

Slit-lamp and ophthalmoscopic examination showed that no marked permanent change resulted from injection of hyaluronidase. It seemed possible that disaggregation of the viscous jelly of the vitreous humour might be reflected in changes in the intra-ocular pressure. Records of intra-ocular pressure were studied in five rabbits of the series, using a Maclean's tonometer. The tension of the eye injected with inactive hyaluronidase was also recorded, as the tension of the normal rabbit eye can vary

considerably. Injection of active hyaluronidase caused a reduction in tension to about half that of the eye injected with inactive hyaluronidase, within 24 hours of injection. Tension stayed at this level (10—11 mm. Hg) for three to four days, but was back to normal again nine days after the injection. One cannot say whether this reduction in tension is due directly to hydrolysis of the viscous hyaluronic acid of the vitreous humour, or to the resulting inflammation of the eye, but as little change in tension occurred in the control eye injected with inactive enzyme, it seems probable that some of the fall in tension was due to the change in state of hyaluronic acid in the vitreous humour.

SUMMARY

1. The hyaluronic acid in the vitreous humour is disaggregated by hyaluronidase injection and remains so for at least a month. After this time aggregated hyaluronic acid is found, showing that hyaluronic acid can be produced in or secreted into the vitreous humour during life.

2. Injection of rabbit testis hyaluronidase preparations into the vitreous humour of the rabbit caused a prolonged inflammatory reaction, noticeable within two hours in the aqueous humour and after 24 hours in the vitreous humour.

3. The nitrogen contents of both vitreous and aqueous humours are increased after hyaluronidase injection.

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BILATERAL CONGENITAL ANOPHTHALMOS*

BY

F. PAPOLCZY

BUDAPEST

ANOPHTHALMOS is one of the rarest of the developmental anomalies of the eye and it is usually bilateral. In the case described below an orbital cyst and other developmental anomalies were present.

Congenital anophthalmos was first described by Lyscostenes and later by Schenk (1609) and Barthelin (1657), but Briggs was the first to mention the hereditary character of this disease (Sorsby, 1934). At the beginning of the nineteenth century Briggs described a family in which, out of seven children of healthy parents, three were born with bilateral, and one with unilateral anophthalmos. Later Monteath (1821) and Walker (1831) emphasized the hereditary nature of the disease.

Manz (1876) says that in most cases of congenital anophthalmos rudiments of the eye can be found in the orbit. When this is not the case, however (Röder, Gradenig), the optic nerve is imperfect; it may be represented by strands of connective tissue, or it may be absent (Rudolphi). The foramen opticum may be constricted. Rudolphi claims that it is impossible to distinguish exactly between this picture and microphthalmos, and that anophthalmos is not a developmental defect of the eye, but atrophy due to some unknown injury in foetal life. He believes the pathogenesis of microphthalmos and anophthalmos to be the same.

Landesberg (1877) pointed out the importance of blood relationship between the parents. Hippel (1899) showed that cases of microphthalmos and of bilateral anophthalmos can occur in the same family.

Recent reports tend to confirm these earlier views. Cecchetto (1920), Ougaud (1922), Langon (1926) and Wirth (1938) all mention the parents as being related by blood. Hanke (1904), in a case of congenital bilateral anophthalmos could find rudiments of the eye, consisting of very small choroidal remnants embedded in fibrous connective tissue only by histologic examination after death. The infant had neither optic nerve nor tract on either side. Triepel (1920) reports that in his case there was atrophy of the optic nerve and chiasm. Gallemaerts (1924), in a case of bilateral anophthalmos found, after histologic examination, rudiments of the eye on the left side only; on the right side there were no traces of the eye.

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* Received for Publication, May 5, 1949.

Neither side had optic nerve, or chiasm ; the corpora quadrigemina were defectively developed. Ougaud (1922) studied a family in which anophthalmos, choroidal coloboma and interstitial keratitis occurred. Canneyt and Vandemeulebroecke (1937) found unilateral and bilateral anophthalmos, microphthalmos and iris coloboma in four generations of one family. Wirth (1938) gave the history of three generations of a family with unilateral and bilateral anophthalmos, coloboma of the iris, the choroid and the crystalline lens, and congenital cataract.

In 1948, in this Journal, I presented the case of a ten-day-old boy with right-sided anophthalmos and orbital cyst, together with other developmental anomalies (proboscis on the right side, hare-lip and cleft palate). The rudiments of the eye were apparent only by histological examination of the contents of the orbit. Soon afterwards, the children's ward of our hospital, from which this patient had come, sent a six-months-old boy with congenital bilateral anophthalmos to the eye-department for examination.

FIG. 1.

FIG. 2.

1 He was the second child of a healthy mother of 22 years of age. The parents were not related. Wassermann reaction was negative. No developmental anomaly had ever occurred in the family.

Ophthalmological report:—Lids sunken on both sides, palpebral fissure shorter than normal (9 mm.), no eye on either side conjunctival sac very narrow. Rudiments of the eye neither visible, nor palpable. No other developmental anomalies. (Figs. 1 and 2).

X-ray examination:—The bony wall of the orbit, as well as the optic canals much narrower than usual on both sides. In profile the forehead appeared flattened, the cranial basis shortened, the three cranial *scalae* situated on one level. The sella smaller than normal, but clearly defined. Encephalography revealed no essential anomaly.

The child being alive and well, there was neither *post-mortem* nor histological examination.

According to the literature, in cases of congenital anophthalmos there is generally a record of blood relationship between the parents or a family history of anophthalmos or other developmental anomalies. It may happen, however, as in the cases of Hasner (1876), Wicherkiewicz (1899), Hanke (1904), Triepel (1920), Ventola and

Zembrano (1946) that neither were the parents related, nor—which is more important—did the condition appear to be hereditary or associated with other developmental anomalies. This is not inconsistent with the hereditary character of the disease. It may be that the parents cannot give exact information about their family history; moreover, the child afflicted with anophthalmos may become the founder of a family suffering from this or some other developmental anomaly.

By clinical examination I could not detect rudiments of the eye on either side. But it has been shown in the literature that when the child dies and *post-mortem* or histological examination can take place, rudiments of the eye are usually found in the soft parts of the orbit. From the X-ray examination we may deduce that the optic nerves or perhaps the chiasm and tracts were defectively developed but positive radiological proof of this is lacking.

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A THERAPEUTIC STEP IN CHRONIC GLAUCOMA*

BY

G. DE L. FENWICK

A MEASURE that is sometimes very useful in treating an attack of acute glaucoma is the retrobulbar injection of novocain (procain), administered not pre-operatively, but as an isolated therapeutic incident (S. Gifford, M. J. Icaza). It does not of course have a permanent effect, so that an operation becomes necessary sooner or later; but the object of the injection is to avoid the performance of

* Received for publication, May 23, 1949.

a Graefe iridectomy on a haemorrhagic painful eye, in a sick exhausted patient; for the results of these operations, whether done with local or general anaesthesia, are inferior to those of the "quiet" glaucoma operations, leisurely performed. Retrobulbur injections have certain risks, of which the chief is retrobulbar haemorrhage, but it is believed that this danger can be eliminated by the use of a specially designed needle. These matters will be discussed later in this paper.

The following histories demonstrate the possibility of success with this treatment; others could be quoted in which it was entirely without effect; why it succeeded in some cases and not in others is not known. Accurate statistics are not yet available, but it appears that the injection will produce the desired result in about one quarter of the cases in which it is tried; the desired result being the establishment not necessarily of normal tension, but of a comfortable white eye which can be trephined in due course.

CASE HISTORIES

1. I., female, aged 64 years, came to Moorfields August 5, 1947, with pain in R. eye of 2 weeks duration; typical acute glaucoma, VA=4/60; treated with 1 per cent. oily eserine and heat every 15 minutes, but after several hours of this there was no improvement whatever. Was then given a retrobulbar injection of 1 c.c. of 4 per cent. novocaine containing 0·1 c.c. of 1/1000 adrenalin and eserine was resumed; his pupil soon contracted, his pain subsided and his tension fell, though it was not normal until next day. The eye was trephined in March, 1948, with a satisfactory result.

2. J.G., male, aged 60 years, attended January 6, 1949, with a pain in R. eye which had lasted 8 days; congestion, corneal oedema, shallow A.C.; tension (digital) = "+" (35 to 50 Schiötz); VA = counting fingers; L. eye blind; was treated with eserine and heat, as in Case 1, but without any improvement, was then given a retrobulbar injection as above, which reduced the tension to normal in an hour. Eserine was continued, but next day the tension began to rise again. On the third day the injection was repeated (this time without adrenalin), the tension again fell to normal, the eye whitened and was trephined an hour later; VA=6/6.

3. A.P., aged 56 years. Onset of acute glaucoma in L. eye October 22, 1948; intensive eserine and heat treatment instituted the same day but without effect; next day was taken to theatre and given 1·5 grm. sodium pentothal intravenously, as this anaesthetic, when previously used for glaucoma iridectomy, had been observed to reduce the tension; it fell very slightly and then became stable; half-an-hour later, retrobulbar novocaine and adrenalin were given and considerable improvement was almost immediately evident in cornea, pupil and tension. He returned to bed and the improvement was maintained. November 2, L. trephine, December 11, VA=6/9.

DISCUSSION OF CASES

In Case 2 the tension fell after the first injection, only to rise later, presumably because of absorption of the novocaine. A second injection reduced it again, and the operation was performed without delay lest it should rise a third time. Perhaps in this case, after the first injection had reduced it, it could have been kept down by the use of miotics other than eserine; for Scheie and Ojers believe

that retrobulbar novocaine, by paralysing the ciliary ganglion, inhibits the formation of acetyl-choline in the pupillary nerve-endings, and so renders eserine (but not pilocarpine) ineffective. However, in the present writer's brief experience, eserine has been observed to maintain pupillary constriction after cataract extraction, even though a complete extra-ocular paralysis had been pre-operatively induced.

In Case 3, one cannot say with certainty how much the fall in tension was attributable to the retrobulbar injection and how much to the pentothal, but it seemed to be largely due to the former.

Dangers of Retrobulbar Injections

1. The chief danger is *retrobulbar haemorrhage.* See below.

2. *Transient blindness.* This has been described by Ida Mann, occurring in an otherwise healthy woman aged 35 years, after retrobulbar novocaine-adrenalin for repair of a retinal detachment. A few weeks later the same injection was given (for a second operation), but this time without harmful effect; the operation was successful, the visual acuity being 6/6. The temporary blindness was thought to be caused by the needle-tip piercing the sheath of the optic nerve and allowing the solution to infiltrate its fibres. Bidault saw a similar occurrence in a patient with senile macular lesions. He attributed it to constriction either of the central retinal artery or of other vessels entering the optic nerve from the opththalmic artery.

3. The injection is usually said to cause pupillary dilation. This would be a disadvantage in glaucoma, but appears to be only a theoretical one.

4. The optic nerve might be damaged in clumsy hands.

5. Orbital infection. This is, or should be, unthinkable.

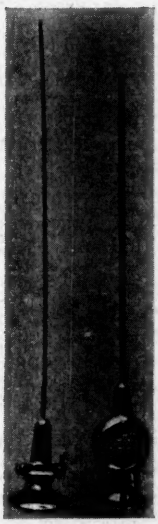
Retrobulbar Haemorrhage

In the Moorfields theatres some six haemorrhages are seen every year—*i.e.*, one haemorrhage in about 160 injections. The majority of these injections are given for cataract or detachment operations, but even for these non-urgent procedures a haemorrhage (and the necessity to defer the operation) may have unsatisfactory results; as in the case of a nervous patient who after such a postponement, could never be persuaded to enter the theatre again. If the postponed operation is urgent, as in acute glaucoma, the situation can be more serious; two cases are known to the writer: in the first, the haemorrhage necessitated a postponement of an urgent glaucoma iridectomy for five days; as a result, this patient left hospital with extremely poor vision. In the second, likewise, iridectomy had to be deferred, but happily the glaucomatous attack subsided and the

patient went home with an efficient (though black) eye; such good fortune would be exceptional.

Traquair believed that haemorrhages could always be avoided by slow careful injection, and many surgeons hold the view that if the solution is being constantly forced out of the advancing needle, it is impossible to enter a vessel. However, haemorrhages have occurred even when these criteria were fulfilled. One would expect them to occur more often if the needle point is passed to the very apex of the orbit (as recommended by H. Gifford), for here the vessels are larger and more fixed; one would also expect them more often in inflammatory conditions because of orbital congestion. Goulden considered that the incidence could be reduced by using a needle with a slightly blunt point.

To reduce the risk of haemorrhages, a blunt needle with a sharp stylet has been designed.



Length of needle ... ... 50 mm.
External diameter ... ... 0·7 mm.
Base ... ordinary Record syringe fitting.

Technique of Retrobulbar Injection

The needle with the stylet in it is passed through the skin in the usual infero-temporal position just inside the orbital margin. This takes more pressure than with an ordinary retrobulbar needle because of the shoulder and the greater diameter; in a hypersensitive patient, therefore, a few minims of novocaine could be injected into the skin first; but this is not usually necessary if the stylet is really

sharp. The needle and stylet are now advanced until one feels the orbital septum being pierced. As soon as this is passed, the stylet is withdrawn, and the blunt-ended needle can now be moved on safely. Often the needle-tip is felt meeting another fascial layer—the sheet that extends between the lateral and inferior recti. If pain is experienced here one can fit the syringe to the needle and inject 0.5 c.c. of novocaine before proceeding. After this sheet has been passed, the end of the needle lies within the muscle cone (the ideal position for it is 2 mm. below and behind the posterior pole of the eye) the ciliary ganglion lies some 7 mm. behind the posterior pole, so if the needle-tip is in this situation, the solution flows into this 7 mm. space and infiltrates the ciliary nerves and ganglion. 1.5 c.c. of 4 per cent. novocain are used. It usually contains 1/1000 adrenalin, 1 minim to the c.c., but in case 2 described above the second injection was successful without adrenalin. It seems doubtful whether adrenalin is essential to its success, and occasionally it has produced alarming anginal reactions. It is not suggested that this needle should be used for every retrobulbar injection, but only where it is particularly important to avoid a haemorrhage.

Rationale

We do not know how retrobulbar novocaine relieves an attack of acute glaucoma. Its effect could be due to:

(*a*) Extra-ocular muscle paralysis. The fall in tension that occurs after ordinary pre-operative retrobulbar injections (as for cataract extractions) is attributed to this, but it cannot be important in acute glaucoma.

(*b*) Inhibition of parasympathetic activity. This explanation is not easily supported anatomically; for the only para-sympathetic fibres that are known to pass to the eye are those that terminate in the sphincter pupillae and ciliary muscle, and inhibition of these would be expected to aggravate narrow-angle glaucoma, not relieve it. There is no evidence that any vasodilatator fibres supply the eye (Duke-Elder).

(*c*) Inhibition of sympathetic activity. Thiel found that the tension in glaucomatous eyes was reduced by ergotamine. This drug, though vasoconstrictive, is in general antagonistic to adrenalin and sympathetic activity, and he concluded that glaucoma may be due to an increase in sympathetic tonus. If this were so, the success of retrobulbar injections would be a fairly logical consequence.

(*d*) Interruption of Reflexes. It seems possible that the injection reduces the tension by breaking two reflex arcs. One of these is a conscious cycle—the increasing pain of acute glaucoma induces a mental state which aggravates the tension. The other one is autonomic, but its exact pathways are not known (*b* or *c*, above). Probably an important part in the aetiology of acute glaucoma is played by axon reflexes (*i.e.*, local reactions in the eye, liberating histamine); but these reflexes occur whether the main sensory trunks are intact or not, so they do not explain the beneficial effect of the injection. However, the mechanism may be similar to that of causalgia. In this disorder there is, in the affected limb, pain and

congestion which may be relieved by the injection of anaesthetic solutions into the trunk of the sensory nerve concerned. Lewis suggests that the symptoms of causalgia are due to release of histamine-like substances in the skin as a result of abnormal impulses passing in a centrifugal direction along the affected sensory nerve.

Conclusion

It is suggested that a retrobulbar injection of novocaine should be tried in all cases of acute glaucoma which are not improving after 24 hours of the usual intensive treatment—miotics, counter-irritants and sedatives. The chief danger of this measure, *viz.*, retrobulbar haemorrhage, has, it is hoped, been eliminated by using a needle on the trocar-and-cannula principle.

Summary

1. Some cases of acute glaucoma can be terminated by a retrobulbar injection of novocaine; three such are described.
2. The risk of an orbital haemorrhage is important.
3. This can be avoided by using a special needle.
4. The rationale of the procedure is discussed.

Acknowledgment

It is a pleasure to record my deep gratitude to the Moorfields surgeons who have assisted me and given me permission to describe their cases, particularly Miss Ida Mann, Mr. F. W. Law, Mr. A. Lister and Mr. M. H. Whiting.

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EARLY POST-OPERATIVE DETACHMENT OF THE CHOROID*

BY

FRANCIS CSILLAG

BUDAPEST

EARLY post-operative detachment is a secondary and long known phenomenon. It occurs as an unexpected sequence after cataract, glaucoma, iridectomy, trephine, sclerectomy and cyclodialysis operations. Its incidence, according to the various authors, varies much. The highest percentage is reported by O'Brien, who states that 62 per cent. of his operations were immediately followed by detachment of the choroid.

Origin of the detachment is explained differently by various authors. Fuchs assumes a warping of the choroid, while Meller and O'Brien believe an imperfect healing of the incision to be responsible. Meesmann, Hagen, Urbanek and Fronimopoulos think the post-operative hypotony to be of significance. Lindner is of the opinion that the contracting vitreous body exerts traction on the choroid. Bonnet and Grandclement assume a relationship with existing general or ophthalmological disease. A considerable number of the authors think that behind the detached choroid, blood (Urbanek) or fluid accumulates, but they differ concerning the origin and the active or passive consequences of the same. A transudate from the choroidal vessels is assumed by Hagen, O'Brien, Fronimopoulos and Meesmann, whereas Meller thinks that the ciliary body forms the liquid. H. D. Mayer (1939) states that the aqueous oozing backwards through the loosened attachment of the ciliary body forces the choroid off its base. The cause of hypotony is the increased outflow of the aqueous. If the anterior chamber is well preserved and pressure remains normal, she believes serous exudation to be of importance.

Csillag has emphasized in his lecture (delivered at the Hungarian Ophthalmological Society, 1939), that if during operation a communication is established between the anterior chamber and the supra-choroidal space, the aqueous oozes backwards and detaches the choroid. The increased outflow of the aqueous causes a shallow chamber to form and hypotony to ensue. His lecture has been published late, owing to war-time difficulties.

The choroid adheres to its base only at the head of the optic nerve and where the veins perforate the sclera. The operative deformation of the eye-ball may cause the choroid to become loose and warp at its base (commotio of the choroid). The decrease of

* Received for publication April 11, 1949

pressure may permit transudate from the vessels to enter the supra-choroidal space, gently elevating the choroid (amotio of the choroid). Such a detachment is small and flat, and the fluid behind it is of insignificant amount (O'Brien's frequent detachments seem to have been of this kind). Such detachments should not be regarded as being genuine ones (ablations), as, following reunion of the lips of the incision and re-establishment of intra-ocular pressure, they tend to disappear.

Three different methods of cataract extraction were used at the ophthalmic clinic of Budapest University at a certain time. The origin of the choroidal detachment depended, as the author was able to ascertain, chiefly on the method of incision and partly on that of extraction. The least number of detachments followed incision which was conducted entirely within the limbus (conjunctival apron); they became more frequent following the conjunctival flap method (the incision can be finished sclerally in that case), and the most frequent detachments occurred, despite correct operation and uneventful healing, following Horváth's scleral flap method. Intracapsular extraction and subsequent extraction of the capsule increased the incidence of detachment.

This incidence is demonstrated by the following table:

Method of incision	Intracapsular			Extracapsular			Total		
	extract.	detachm.	per cent.	extract.	detachm.	per cent	extract.	detachm.	per cent.
Conjunctival apron	279	2	0,72	136	1	0.73	415	3	0.70
Conjunctival flap	79	2	2.53	74	1	1.35	153	3	1.96
Scleral flap ...	334	14	4.19	193	4	2.07	527	18	3.41
Total	692	18	2.60	403	6	1.48	1095	24	2.19

Only those cases were investigated for detachment which were conspicuously late in re-filling the chamber. Thus only those cases remained undetected, which required 2 to 3 days in re-establishing the chamber and the detached part was replaced on the 6th to 7th day at a time, when it became possible to examine the eye with a mirror. Therefore we may assume this post-operative complication to be more frequent than is shown in the table above. But all sorts of incision may react likewise and therefore the relative probability and conclusions drawn therefrom remain the same.

Detachment more frequently occurs after complete iridectomy and following basal iridectomy, but there is no considerable difference. Various iris operations have not been included in the table, not being of decisive influence concerning detachment. The extraction has been regarded as being intracapsular when the lens was removed

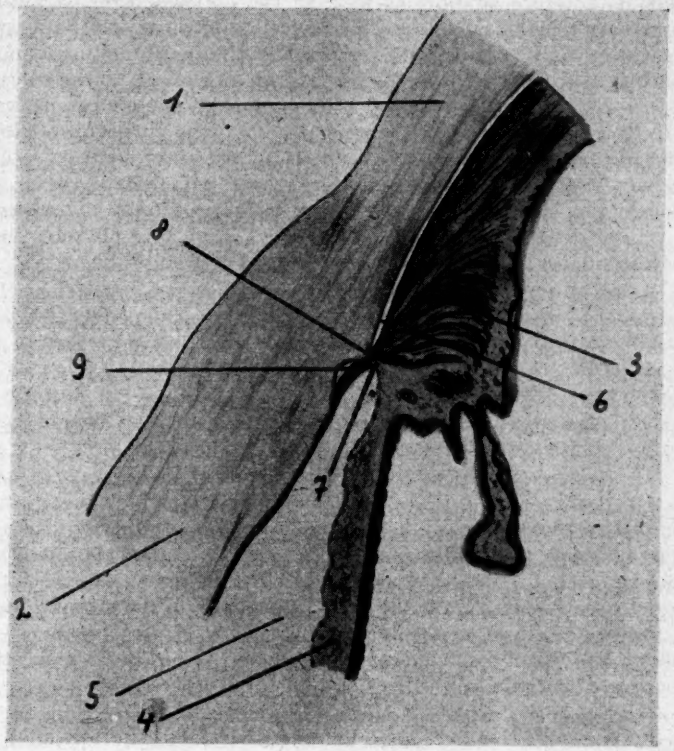
together with an intact capsule. I believe it is unlikely that detachment is influenced by age, sex, ocular alteration or systemic disease.

After cataract extraction the intra-ocular pressure decreases, the vessels of the choroid dilate and gently push the vitreous body forward. As soon as the wound closes, the accumulated aqueous refills the vitreous body and the deep chamber, which characterizes aphakia. The physiological equilibrium between loss and production of aqueous re-establishes itself, and intra-ocular pressure stabilizes. The patients were not examined by a retinoscope on the days immediately following operation. Perhaps this circumstance accounts for the fact that detachments were less frequently noted by us than by other authors, and none of the aforesaid flat detachments called "amotio" occurred. The onset of detachment is shown by the chamber remaining flat for days, and by hypotony. The detachments began in the upper half (or were drawn up there), and proceeded from there downward and backward. Even simple illumination discloses the dark-grey object bulging into the vitreous body, situated next to the ciliary body, which can be trans-illuminated through the sclera.

A conspicuous feature in our cases was a shallow chamber, despite a perfectly closed wound. So a shallow chamber does not necessarily mean faulty healing. Therefore defective filling of the anterior chamber in the case of a well-closed wound, should be ascribed to something else. Our attention was particularly called to the fact, that in cases where the re-establishment of the chamber, due to an imperfect reunion of the lips of the incision, was retarded, though the eye remained soft, the choroid remained in its proper place. With one of our cases, two weeks after intra-capsular extraction, the chamber remained so shallow on account of the filtrating wound, that the bulging membrane of the vitreous body touched the cornea. Two months after operation the chamber was still flat, and ocular pressure was 15 mm. Hg. Nevertheless, the choroid remained *in situ*. Consequently the detachment cannot be ascribed to a leaking wound and subsequent hypotony, because then it should be present in every such case, and again a mal-united wound should characterize every detachment. Actual observation confirms the opposite: detachment is less probable, if the wound leaks outwardly. Nevertheless I do not believe that an outward filtrating wound necessarily excludes detachment.

As the table shows, most detachments occurred following the scleral flap incision. Since this operation differs from the others only by the form of the incision, the cause of detachment has to be sought for in this direction. Before incision within the limbus is finished, by means of Graefe's knife a 3 mm. long and broad flap is cut out upwards through the half thickness of the sclera, as has been described already by Horváth (1939), the originator of this method.

The anterior chamber is separated from the supra-choroidal space only by the trabecular tissue of the angle of the former, and the anterior end of the ciliary muscle attached to the corner of the chamber (see Fig.). The thickness of this part, its distance from



1 The sclera; 2 cornea; 3 ciliary body; 4 iris; 5 anterior chamber; 6 supra-choroidal space; 7-9 anterior end of the ciliary muscle, scleral spur and trabecular tissue of the angle of the anterior chamber (line of cleavage).

the limbus, and the thickness and curvature of the sclera vary in individuals, although only by small differences. On account of this it is rather difficult to cut a 3 mm. flap off in such a manner that it should not contain the entire thickness of the sclera in the form of a central strip. By slicing the sclera, the separating part is easily cut, whereby a small cleft is formed between the anterior chamber and the supra-choroidal space so that both communicate.

As soon as the wound closes, the accumulating aqueous does not press the slightly bulging vitreous body back, and does not form the anterior chamber, but finding less resistance along the communicating intra-ocular way, leaks backward behind the choroid and lifts the latter from its base. The chamber, despite a well-joined incision, remains therefore shallow as long as the aqueous leaks backward. As soon as the incision closes, normalisation of intra-ocular pressure begins but is not completed so long as the continually produced aqueous is absorbed through the choroid, as well as by the physiological way. This explains the high-grade hypotony accompanying detachment. The anterior chamber fills up and the intra-ocular pressure rises as backward leakage decreases. As soon as lateral seepage becomes less than absorption, detachment decreases accordingly. As the aforesaid communication closes, the aqueous is progressively absorbed beneath the choroid, the choroid sinks back again, and the intra-ocular pressure is re-established.

In five of our cases the anterior chamber was re-established after operation, but emptied after a few days, despite perfect outward closure of the incision. This delayed intra-ocular abortion of the chamber may have been due to the part separating the two cavities having been only damaged by the incision, and not cut entirely; a certain pressure of the aqueous collecting after the wound being closed, is obviously necessary for penetration.

Detachment after intra-capsular extraction is much more frequent, if the attachment of the ciliary body is disturbed by the incision (scleral and conjunctival flap). The traction of the zonular arch may complete the still imperfect communication. This rôle of the zonular arch becomes the more obvious, the more the incision is scleral (see table). Probably a forced traction of the strong zonular arch, together with a simultaneous loosening of attachment of the ciliary body, suffices to cause detachment. Loss of vitreous may sponsor detachment.

Accepting the aforesaid views, we may understand why, in the case of a badly united incision, despite the shallow chamber, no detachment occurs. An imperfectly closed wound does not promote, but rather inhibits detachment, because in the meantime, owing to aqueous loss, the angle of the chamber may close. In one case the detachment occurred 6 days after operation, despite the anterior chamber remaining shallow the whole time on account of an imperfectly united incision. Aqueous seeped without difficulty outwards, and leaked more thoroughly beneath the choroid only after the incision had closed. The choroidal vessels may rupture during operation if the patient's blood-pressure is high. The ensuing haemorrhage may detach the choroid. There were no signs of inflammation associated with the choroidal detachment and no

evidence of any general medical disorder. The intra-ocular pressure before operation was normal. On the basis of these phenomena the author succeeded in inducing choroidal detachment experimentally in animals.

Prognosis of early post-operative detachment is good. The time of complete replacement of the choroid depends on the time elapsing since the complete closure of the angle and on the degree of detachment. It usually takes 1 to 2 weeks. Most authors agree that, if the replacement of the detachment is perfect, no serious consequences follow. I believe that hypotony following operation may even be advantageous for healing of the incision. Prognosis of detachment due to haemorrhage is less favourable. Verhoeff, Filatov, Averbach, and Vail succeeded in saving some sight by instantaneous scleral puncture following an expulsive haemorrhage.

Views on treatment vary. Müller recommends puncture to avoid functional disturbance. Elschnig also stated that a rapid cure followed puncture of choroidal detachment cases which had persisted for weeks after operation, but he recommended it only if the detachment was not due to haemorrhage, and the peripheral circulatory system was in perfect condition. Löhlein proposed cauterisation of fistula-forming wounds. Axenfeld proposed compresses. Imre was satisfied by the effect of pilocarpine. He believed that it caused hyperaemia and swelling of the ciliary body, which helped in the closure of the angle of the chamber.

I believe that detachment following glaucoma iridectomy originates in the same way as that following cataract operations. In our cases following trephine and cyclodialysis detachment also occurred repeatedly. In my experience, anti-glaucoma operations accompanied by detachment were always successful, the eye becoming hypotonic. In case of tissues becoming opaque by operative haemorrhage or pressure following glaucoma operation, examination for detachment is inhibited; furthermore, it is hindered by the narrowness of the pupil, or peripheral position of the detachments. The opening of the filtration angle by cyclo-dialysis is violent and blunt, and any ensuing haemorrhage may soon obstruct the path of the aqueous. This circumstance may account for the comparative rarity of detachment following this operation.

Imre sometimes used scleral puncture by electro-cautery for glaucoma, and this was sometimes followed by choroid detachment. The cauterisation of the sclera softens the eye, and choroidal detachment is a post-operative complication. Closure of the wound increases the intra-ocular pressure. In this case no backward seepage of the aqueous can be assumed, as the operation is remote from the filtration angle. Detachment in such cases is of different origin. It is not only promoted by decrease of intra-ocular pressure,

seepage of the vitreous body, and its shrinkage, but the haemorrhage and transudate elicited by thermic effect elevate the choroid. In choroidal detachment caused by backward seepage of aqueous, as described above in connection with cataract and glaucoma operation, hypotony stops only after the choroid is replaced, whereas in the case of ignipuncture the intra-ocular pressure increases, despite the persistance of the detachment, even after the wound has closed.

Summary

The onset of choroidal detachment following cataract extraction is influenced by the type of incision, the method of traction and by the auxiliary manipulation applied. If during operation the supra-choroidal space is opened by the incision, a communication between the anterior chamber and the former is established. The aqueous oozes backward beneath the choroid, and raises it from its base. Therefore the chamber is shallow, despite the incision being closed towards the palpebral aperture. Hypotony of the detached eye is due to the constant absorption of the aqueous. As soon as the filtration angle is closed, the backward leakage of the aqueous stops, the chamber is re-established, the intra-ocular pressure becomes normal; the fluid from beneath the choroid becomes absorbed, slowly the choroid becomes replaced and no further damage is done. Similarly are explained detachment following anti-glaucomatous operations.

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PRIMARY TUMOUR OF THE OPTIC NERVE*
(Glioblastoma Multiforme)

BY

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PRIMARY tumours of the optic nerve are rare. Nordmann states that Hidan estimates their frequency at 1 :25,000 patients, Bennett at 1 :35,000 and Lundberg at 1 :68,000. Duke-Elder (1940) refers to information from Moorfields (Collins and Marshall, 1900) from which it appears that only two such cases were found among 388,000 patients, and that approximately 350 had been reported in the entire literature. Nordmann further states that Morax (1926) found only three cases of tumours of the optic nerve among 61 neoplasms of the orbit. In 1930 Mathewson pointed out that 80 per cent. of optic nerve tumours were gliomatous, and originated from the nerve itself, while the rest originated from the nerve-sheaths.

The first complete description of such a tumour was given by v. Graefe (1864), but much work has been done since that time in order to clarify the clinical picture of this condition, especially as regards the pathological findings and the terminology. The following quotations from Duke-Elder, however, suggest that considerable confusion still exists: "The nature of the neoplasms, however, remained controversial and in the earlier literature an amazing confusion of terminology is encountered: glioma, gliosarcoma, fibroma, fibrosarcoma, myxoma, myxosarcoma, sarcoma, neuroma, endothelioma, fibromatosis, and so on. They were variously considered mesoblastic or epiblastic, benign or malignant, a hypertrophy or a neoplasm, the pathological diagnosis being changed from time to time and different views being expressed as to their significance and prognosis." It therefore seems justifiable to report a case of optic nerve tumour and to discuss the problems of exact diagnosis.

Case Report. E.G., a 43 year-old woman, was admitted to the Eye Clinic with the diagnosis of orbital tumour. During the preceding four months the patient had noted a marked decrease in vision of the left eye, and simultaneous protrusion of the eye-ball. There was no history of pain or diplopia other than headache, and she stated that she had been perfectly well and able to do full-time work.

Physical examination, August 22, 1941. The patient appeared to be in good general condition. Local examination revealed the left eye protruding more than the right. Exophthalmometer readings were 21 mm. in the left eye and 18 mm.

* Received for publication, March 16, 1949.

in the right. The left eye could not be pressed into normal position. The mobility of the eyes seemed to be normal. No tumour could be palpated in the orbit. There was no evidence of metastasis to regional lymph nodes, nor any pulsation or *bruit*. The left eye was normal as to the cornea, anterior chamber and iris. The pupil reacted indirectly to light. Ophthalmoscopy demonstrated a mushroom-like disc, protruding approximately 9 dioptres. The retinal vessels were enlarged and tortuous, and there were several retinal hemorrhages.

The right eye was normal. Visual acuity: R. 5/5; L. amaurotic. Visual fields: Normal. Intra-ocular pressure: R. 24; L. 14 mm. Hg. Laboratory tests: Urinalysis negative. Serology (Wassermann) negative. Roentgenogram demonstrated a normal skull, left orbit and optic foramen. A week later another roentgenogram revealed a slight widening of the left optic foramen. On September 10, 1941 the patient was dismissed without treatment, but she was ordered to return at regular intervals. Approximately five months later the patient was admitted to the clinic for an examination as the left eye had become red and painful. *Physical examination January* 23, 1942: The protrusion of the left eye was unaltered, but the mobility was somewhat reduced.

L. eye: There was ciliary congestion with the beginning of a *caput medusae*. The cornea was clear. The iris was hyperaemic and showed small haemorrhages Ophthalmoscopically there were no significant changes from August 22, 1941. R. eye: Normal findings. Vision 5/5. Visual field normal. The intra-ocular pressure now was 24 R., and 33 mm. Hg. L. Roentgenogram was taken on January 1, 1942, with the report that since August 8, 1941, a definite widening of the left optic foramen had appeared, and that the outlines of the foramen were blurred.

Summary of examination:

(1) Proptosis of the left eye straight forward and irreducible.
(2) Complete failure of vision had developed simultaneously with the protrusion.
(3) Papilloedema with haemorrhages.
(4) No history of diplopia. Mobility was at first normal, but decreased slightly.
(5) Pain in the eye occurred in association with increased ocular tension.
(6) Widening of the optic foramen over a period of approximately five months.

The patient had been in good health, and there was no evidence of any other diseases.

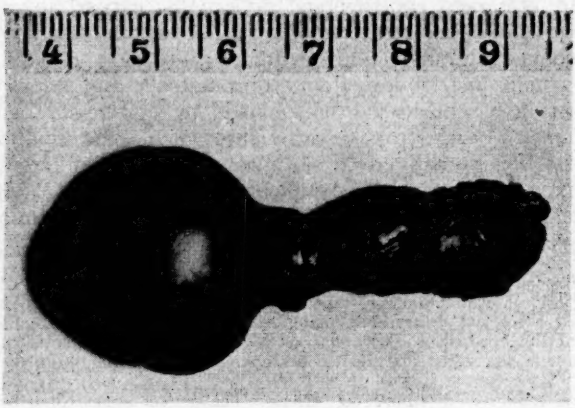

FIG. 1.

The enucleated eye with fasciculus opticus, which has circular constrictions and spool-like swellings.

These findings indicated a tumour of the left optic nerve.

As the eye was afflicted with increased intra-ocular pressure, blindness and pain, we decided to excise it together with the suspected tumour. During the operation one could feel enlargement of the optic nerve with scissors, and by drawing the eyeball forward as much as possible, one had the impression of cutting the nerve behind the tumour. A subsequent pathological examination demonstrated that removal of the tumour had been incomplete. The patient was told this, and

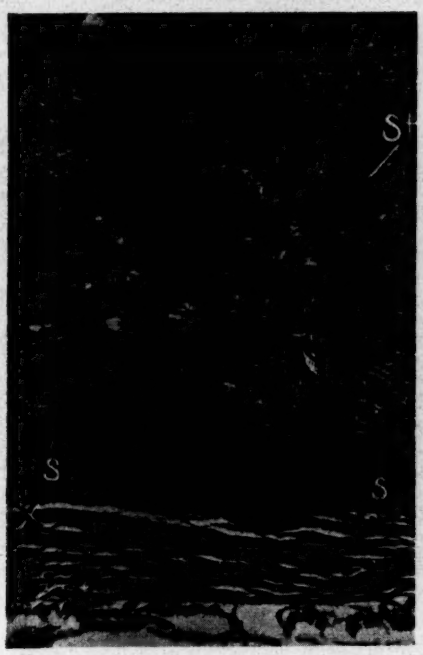

FIG. 2.

Expansively growing tumour limited to fasciculus opticus, which is surrounded by leptomeninges (x) and dura (D). Septa (St) with abundance of connective-tissue and blood-vessels give the tumour tissue a lobular appearance with some dense areas of small cells (s-s). Paraffin preparation. Hematoxylin-eosin staining. Magnified ×73.

that an intra-cranial operation would be necessary. She opposed this proposal, and was then dismissed from the clinic one month after the operation, during which time she received X-ray treatment. She was also advised to continue with X-ray therapy in her home town.

The patient subsequently returned twice for control during the first six months. She had felt well, and, was working at her farm. The other eye was normal, and there were no signs of intra-cranial complications. She now failed to return for her appointment, and her physician reported that the patient died one year after the operation, with increasing cerebral symptoms. No autopsy was performed.

After operation the enucleated eye and the tumour were sent to the Pathological Laboratory of the University Clinic. Dr. Jan Cammesmeyer made the following report: Fasciculus opticus is approximately 3·5 cm. long, and its thickness varies from 0·8-1·3 cm. (See Fig. 1.)

The considerably enlarged fasciculus opticus shows a few circular constrictions. The rostral part is circularly constricted, and in a longitudinal section the tumour seems to be separate from the bulbus. The tumour is of a yellowish-white colour, mainly round, and is entirely surrounded by a capsule. It is of hard elastic consistency. The wall of the eyeball is not infiltrated.

Microscopic examination showed that the dura mater surrounding the fasciculus was not infiltrated by tumour cells. Lymphocytes and fibroblasts fill the interfibrillar spaces of the leptomeninges. The intrameningeal fissures are obliterated by expansion of the tumour. The original structure of the fasciculus opticus is

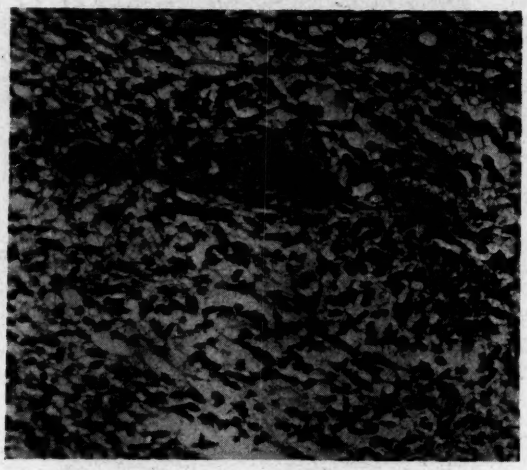

FIG. 3.

Polymorphous tumour tissue without definite polarization of the cells. Paraffin preparation. Hematoxylin-eosin staining. Magnified ×180.

completely replaced by a neoplastic tissue rich in polymorphic cells. Irregular lobules of tissue are limited by occasional vascularized broad fibrous septa which split up the fasciculus as far as the lamina cribosa.

The number of cells varies considerably in the different parts of the tumour. In the central portion of the longitudinal section through the fasciculus, and in some places near the surface there are areas with densely packed, relatively small cells with round, hypochromatic nuclei (Fig. 2).

Other lobules are not quite so rich in cells, and here the individual cell outlines are more clearly demonstrated (Fig. 3).

There is considerable variation in the shape and size of the individual cells as well as in their nuclei (Fig. 4). Various numbers of cytoplasmic processes arise from the different cells, and in some places fuse with the adventitia of the vessels. Besides the unipolar, bipolar and tripolar cells which resemble immature glial cells, spongioblasts and astroblasts respectively, one sees multipolar cells with a better developed cytoplasmic pericaryon which resemble mature astroglia. The

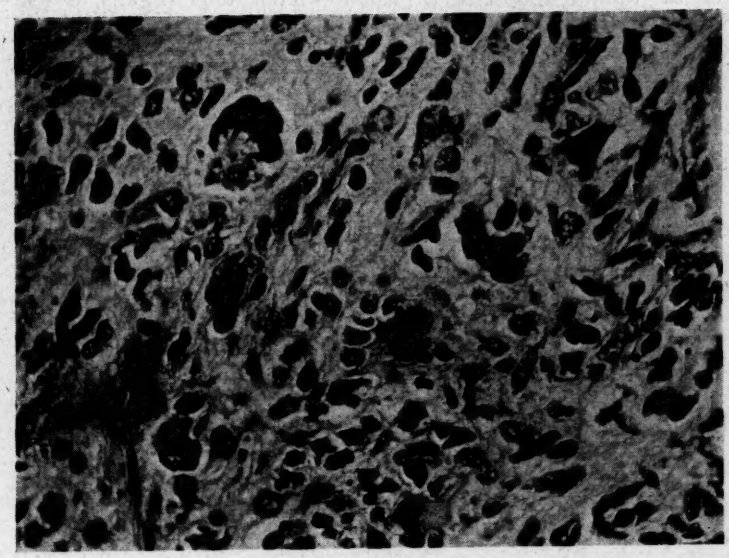

FIG. 4.

Slide demonstrating the variation in size, shape and staining reaction of cells and their nuclei. Note also the tumour's giant-cells. Paraffin preparation. Stained with hematoxylin-eosin. Magnified ×400.

cells show no definite orientation, giving off their processes in all directions, although these are often closely related to the perivascular membranes. Some of the nuclei are very large. Mitoses are frequent, and occasionally incomplete. Multi-nucleated forms are also present.

In one area of the cross-section of the cerebral portion of the nerve the tumour tissue is looser and infiltrated with a number of glial fibres. Palisade formations of pyknotic nuclei surround small, oblong, circular and triangular areas of necrosis. Besides these distinctly degenerated areas one can see throughout the whole tumour tissue small areas of various size in which the cells are not degenerated but show definite pyknotic nuclei.

There are mild reactive changes in the vessels in some places, with increase in the number of endothelial nuclei.

No nerve fibres were found in the paraffin sections examined, nor were there any melanin-pigmented cells.

Conclusion: In the pathological examination of the thickened fasciculus opticus an expansively growing and polymorphic tumour is found, with numerous primitive cell-forms of gliomatous types, continuing to the edge of the resection. Diagnosis: Glioblastoma multiforme.

Discussion: As no symptoms or signs were found indicating

that the tumour might be a metatasis from other organs, it was presumed to be primary. As mentioned above, uncertainty exists as to the classification of the optic nerve tumours. Hence it has been particularly difficult to decide upon the origin of the various neoplasms, e.g., whether they were intraneural (ectodermal) or whether they originated from the inner nerve-sheaths (mesodermal). Rönne (1931) holds that this confusion originates from the fact that in a great number of cases the nerve and its inner sheath are both affected.

Hudson (1912) divided these tumours into three types: I, Gliomatous; II, Endothelioid and III, Fibromatoid, of which the first originated from the nerve itself, and the last two from the sheaths.

Duke-Elder (1940) gives the following classification: I, Essential (Ectodermal) tumours of the nerve—Gliomata; II, Meningiomata, mesodermal tumours of the sheaths. (*a*) Endotheliomata and (*b*) Fibromata; III, Neuro-ectodermal tumours. (*a*) neurinomata and (*b*) malignant melanomata.

Although doubt may exist as to the exact pathological diagnosis in the present case, it most likely belongs to group I, gliomata. The microscopic picture is, however, characterized by considerable polymorphism, and therefore the diagnosis glioblastoma multiforme is made. It also appears that the leptomeninges were infiltrated by lymphocytes and fibroblasts, while the dural sheath was free. Likewise the eyeball itself was not infiltrated, but the tumour spread backward to the brain. In contrast to gliomata, the endotheliomata usually show a marked tendency to infiltrate the dural sheath and hence grow into the orbit. There are, however, some peculiarities in the clinical course of this case. In the literature it is stressed that the gliomata are of such slow development that they may even be considered benign. In the present case the progress of the tumour was rapid, and death occurred approximately two years after the onset of symptoms. In harmony with this view is the widening of the optic foramen on repeated roentgen examinations during five months.

The disease appeared in the present case at a relatively late age, 43 years. Other authors have shown that gliomata of the optic nerve usually start at an earlier age. Hence, Hudson (1912) found that 75 per cent. of the cases occurred in the first decade, and in 88 per cent. before the age of 20. The same author mentions also that endotheliomatous tumours, in contrast to the gliomatous, usually appear later, with an average of 35 years.

The other signs were as expected in this type of optic nerve tumour. Exophthalmos was present in a moderate degree. The

proptosis was straight forward, which is typical of optic nerve tumours and an important sign in the differential diagnosis from other orbital growths. Failure of vision, which in the present case occurred simultaneously with the proptosis, progressed rapidly to blindness. This is a usual feature in these tumours, and Braunschweig (1895) demonstrated that 33 of 44 cases with optic nerve tumours were amaurotic. Reduction of vision in such cases may also be due to secondary changes, e.g., papilloedema and haemorrhages. As the affected eye was blind at the first examination, no defect in the visual field was found. At an earlier stage such may be found, and by spread of the disease to the chiasma, such a defect may even be found in the other eye.

Diplopia is rare in this condition, and this accords with the fact that mobility of the eye may long remain unimpaired. By the time mobility is retarded, the eye may be amaurotic, and hence this symptom is precluded. In the present case there was no history of diplopia.

Most gliomatous tumours of the optic nerve originate in the intraorbital part of the nerve. The rule is that they tend to grow neither into the dural sheath nor into the eyeball. On the other hand they frequently tend to grow backwards through the optic foramen and towards the brain. This tendency leads to widening of the optic foramen, an important sign, which was noted in this case.

Prognosis and Treatment: In spite of the fact that gliomatous tumours of the optic nerve usually develop slowly, the danger of intra-cranial extension exists. Likewise the exophthalmos may become so pronounced as to induce necrosis of the cornea and panophthalmitis.

As these tumours do not as a rule metastasize, radical excision carries a good prognosis. Early diagnosis and adequate removal are important. As these tumours seldom infiltrate the eyeball itself, they may be removed without excising the eye. The usual techniques are those of Lagrange, Knapp and Kroenlein. As all these methods greatly damage the vessels and nerves, subsequent excision of the eye is frequently indicated.

If widening of the optic foramen, suggesting intra-cranial extension of the tumour, is found, or if it is evident that the tumour has been incompletely removed, an intra-cranial operation is advisable (Dandy, 1922; Martin and Cushing, 1923). Before this second operation is done, however, the wound of the first should be healed. This precaution is advised in order to prevent infection and loss of cerebro-spinal fluid. For the same reason secondary enucleation after a cerebral operation must be postponed.

Both Rönne and Duke-Elder are more optimistic in their statements concerning similar cases. Thus Rönne says: " Auf Grund der relativ grossen Benignität der Sehnerventumoren kann das Operationsresultat befriedigend sein, selbst, wo eine völlige Entfernung des Gewebes am Foramen opticum nicht gelingt."

SUMMARY

The case of a 43-year-old woman with a " glioblastoma multiforme " of the optic nerve is given.

The usual symptoms and signs of such a tumour were present. A widening of the optic foramen was found on repeated roentgengrams. The tumour was excised together with the bulbus. Unfortunately pathological examination revealed that the operation was incomplete. The patient refused to have a secondary intra-cranial operation. In spite of post-operative X-ray therapy she died one year later from intra-cranial complications.

The pathological picture was characterized by polymorphism, and the diagnosis was " glioblastoma multiforme." The tumour was considered to be primary.

Unusual features in this case were the appearance of the tumour at a relatively late age, its rapid course and its polymorphism.

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AN INCOMPLETE FORM OF MANDIBULO-FACIAL DYSOSTOSIS (FRANCESCHETTI'S SYNDROME)*†

BY

GY. P. HALBERG *and* J. M. PAUNESSA

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IN 1944, Franceschetti and Zwahlen (Geneva), after a careful study of the literature, gave a detailed description of two cases of a new symptom-complex affecting the bony structure of the face: mandibulo-facial dysostosis. On studying these cases, it became apparent that a new set of well-defined clinical and anatomical signs was common to all those afflicted with this dysostosis. It is due to Prof. Franceschetti who correlated the symptoms and signs of isolated cases, that the condition is now recognised as a well defined ophthalmological entity.

PRESENT CASE-HISTORY

Julio J., a six-year-old boy, was brought to the out-patient clinic because of a convergent squint. The right eye was convergent (anti-mongoloid type) from birth. The use of spectacles did not reduce the angle of squint. The patient's ophthalmological history was otherwise negative.

FIG. 1.

Front view of the patient.

Eye examination :—

Vision.—R. eye: 0,4 without and 0,6 with correction. L. eye: 0,8 without and 0,9 with correction.

Horizontal deviation: on tangent scale +50°; on synoptiscope +55°.

Vertical deviation: L. hyperphoria of 30°.

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† Received for publication, March 30, 1949.

The patient had abnormal retinal correspondence. A pseudo-von Graefe sign was elicited on the left side.

In short, the eye examination revealed convergent strabismus, contracture of the inferior oblique muscle of the left eye, alternating hyperphoria, pseudo-von Graefe sign on the left, bilateral hypermetropic astigmatism, amblyopia of the right eye. We noticed an asymmetry of the face and a resemblance to previously

FIG. 2.

Right profile view of the patient

FIG. 3.

Left profile view of the patient.

observed cases of mandibulo-facial dysostosis. The right side of the face was particularly suggestive of this condition.

This patient was examined along the lines laid down by Franceschetti and Zwahlen (1944) (Figs. 1, 2 and 3):

1. Palpebral fissures, eyelids, eyelashes: There was an obliquity of the palpebral fissures of 20° on the right and 15° on the left. They measured 30 mm. and 26 mm. on the right and left side, respectively. They were triangular in shape by reason of a downward traction of the external part of the lower lid.

This condition was more prominent on the right. The eyelashes consisted of a double row on the lower lids, and were very long on the upper lids.

2. Upper and lower jaws, palate and teeth: The patient had a superior prognathism and a slightly atrophic, receding chin. The palate had an ogival form (Fig. 4). The implantation of the teeth was very anomalous.

FIG. 4.

The palate of the patient.

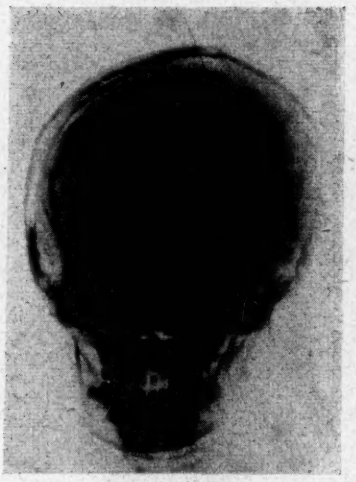

FIG. 5.

3. The malar bones were atrophic, especially on the right, leading to facial asymmetry.
4. The external, middle and internal ears showed no signs of malformation.
5. The naso-frontal angle was completely absent.
6. No macrostomia or fistulae on the cheeks were seen.

X-ray findings (Figs 5, 6, 7 and 8)

X-ray studies showed a marked facial asymmetry. The anterio-posterior diameter of the cranium was increased (dolichocephaly), and the digitate impressions were large and well-formed. The sella turcica was small and showed very clearly a hyperostosis of the sphenoid bone. The sphenoidal sinus was rudimentary and

FIG. 6.

FIG. 7.

of the hypoplastic type. The frontal sinuses were small and hypoplastic. The mandible also showed hypoplasia. The nasal septum and the vomer were deviated. The palate was in the form of a pointed arch. The orbital perimeter was unequal and orbital asymmetry was evident.

FIG. 8.

General physical and mental examinations

The physical and mental development of the patient were normal for his age. The physical constitution of the patient showed a distinct tendency to the adiposo-genital type.

Summary

The examination of a 6 year-old boy gave the authors the opportunity to describe a case of an incomplete form of mandibulo-facial dysostosis (Franceschetti's syndrome).

It was characterised by:

1. Oblique palpebral fissures and dropping of the lower lids, as well as anomalous implantation of the lashes.
2. Superior prognathism and atrophy of the chin.
3. Atrophy of the malar bones.
4. Ears normal.
5. Complete absence of the naso-frontal angle.
6. No macrostomia or fistulae on the cheeks.

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OCULAR ALLERGY IN HANDLERS OF STREPTOMYCIN *

BY

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THE successful results obtained in the treatment of tuberculosis (particularly tuberculous meningitis) by streptomycin, and the low toxicity of this drug have encouraged its widespread use. Special streptomycin centres have been established, and we apply streptomycin treatment on a large scale. Toxic effects of streptomycin are very few nowadays. This must be attributed to the improved purity of the drug and to the wide experience which has been gained in its use. The toxic effects either involve the nervous system and the organs of the special senses or appear as allergic toxic disturbances.

Dermatitis from contact with streptomycin has been noted, chiefly in physicians and nurses who give many injections daily. Since 1947, first in the United States and later in England and France, studies have been published on pathological appearances of the skin and mucous membrane (conjunctiva) of hospital nurses. The study of such cases has proved that the condition was an allergic manifestation of sensitivity to streptomycin. Contact with the drug is either direct, during its preparation or injection, or indirect, from continuous contact with patients and their bedding.

There is no proof that sex plays any part in the appearance of allergy. Nurses seem to be more often affected because their work brings them into closer contact with the drug and with the patients during treatment. No definite allergic tendency is necessary before the appearance of dermatitis. The intra-dermal tests with weak solutions of streptomycin, administered at frequent intervals to nurses, become strongly positive. This confirms the specific allergic sensitivity as soon as the first cutaneous or ophthalmic (conjunctival) signs appear. This specific drug-allergy appears after a period varying from one to six months of continuous contact with streptomycin.

Sometimes general allergic symptoms such as dizziness, headache and fatigue may be noted. These are followed by the manifestation of dermatitis proper which appears mainly on the hands and face. The eyes and their adnexa are most frequently involved. Varying forms and intensities of blepharitis and conjunctivitis appear. First may come the familiar disturbances of blepharo-conjunctivitis,

* Received for publication, March 30, 1949.

i.e., itching, epiphora and injection of the conjunctival vessels, and blepharitis itching provokes an eczematous dermatitis which may become septic. The conjunctivitis sometimes becomes sub-acute or acute, and the conjunctiva and eyelids are very swollen. Sub-acute or chronic forms of this allergic or professional blepharo-conjunctivitis may be found.

The local treatment should be mild and symptomatic. Chief attention should be given to the avoidance of any contact with streptomycin or with patients receiving streptomycin treatment. The period required for the cure of this benign form of allergic dermatitis is variable. Relapses of completely cured cases of allergic blepharitis and conjunctivitis mean that there has been a fresh contact with the drug.

Since the allergic sensitisation of the skin is not general, the selection of an ophthalmic location may be explained either by the immediate contact of the eyelids (through contamination by the hands) with the solution of streptomycin during preparation or by the exposure of the worker's face to the products of evaporation of the drug. Allergic symptoms in persons working with streptomycin appear to be frequent, and according to present statistics involve from 5 to 57 per cent. of those handling the drug. Some protection may be obtained by the use of rubber gloves and protective goggles.

Many cases of this allergic blepharitis and conjunctivitis have already appeared in the special streptomycin centres, *e.g.*, of 110 nurses and two doctors who administered streptomycin intermittently or continuously thirty nurses (27 per cent.) showed allergic reactions. In 25 of them blepharitis and conjunctivitis appeared, and 22 had also dermatitis on the hands. The other 5 developed only dermatitis on the hands. Nurses who prepared solutions of streptomycin continuously over a long period and had allergic tendencies were more seriously affected.

The most severe of these cases was that of a nurse who had a general allergic tendency, and had prepared streptomycin continuously for two years. After she had been cured a severe dermatitis appeared on her hands and eyelids as soon as she began to work again with the drug; the skin reaction to streptomycin became strongly positive.

In another case of blepharitis and conjunctivitis an extensive dermatitis appeared on the exposed side of the neck.

The intra-dermal reactions to streptomycin in typical cases were generally positive, especially in the most severe and obstinate cases.

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CONTACT SHELL APPLICATOR FOR USE AS A CORNEAL BATH*

BY

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INSTILLED eyedrops disappear from the conjunctival sac within a few minutes (Ridley, 1931/32) and if it is desired that the drug should act for a long time, one has to use it in ointment-form (preferably under bandage) or as a corneal bath. Contact shells are also useful for the local application of drugs to the eye (Klein, 1942), and have proved satisfactory during the past eight years.

The contact applicator looks like a rather heavy contact-lens with two studs on the corneal portion. The scleral part has a diameter

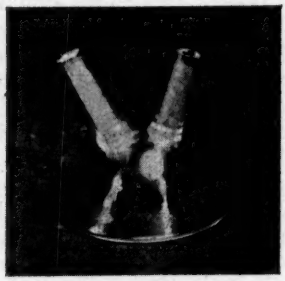

FIG. 1.

of 20 mm. and a scleral radius of curvature of 12 mm. The corneal segment is raised so as to form a chamber for the fluid. The two small studs serve as a handle when inserting the applicator under the lids, and each of them has a bore reaching into the chamber, one for filling up the chamber by means of an eye-dropper, and the other for the escape of air. One drop of half per cent. amethocaine hydrochloride gives sufficient anaesthesia.

To insert the contact applicator the patient is asked to look down, and the upper margin of the contact applicator is slipped under the upper lid. The patient is then told to look up, and the applicator is placed on the eye under the lower lid. Then it is filled up with the solution used for treatment, and the applicator is left in position for the desired period, usually 5 to 30 minutes. If necessary it can

* Received for publication, April 11, 1949.

be refilled. It can be cleaned by washing with soap and water, and chemically sterilized by keeping it in 1:1000 mercuric bichloride or in chlorine solution (Solvellae Chloramine B.P.C. in 4 oz. water) for 15 — 20 minutes, followed by rinsing. Alcoholic solutions, phenolic antiseptics or heat sterilization are not suitable, as they are detrimental to the plastic material of which the applicator is made.

The contact applicator can be used for any solutions such as sulphonamides, mydriatics, miotics, urea, etc. Struble and Bellows (1944 and 1946) have shown that a high concentration of penicillin in the anterior segment of the eye can be built up by the use of a corneal bath, and they have advocated this procedure for the treatment of corneal ulcers, particularly if the deeper layers are involved. In chemical burns the applicator can be used for continuous irrigation with the antidote, such as ammonium tartarate solution in lime-burns. For irrigation a suitably placed flask or undine can be connected with rubber tubing.

The contact applicator is manufactured by Messrs. G. Nissel and Co. Ltd., Siddons Lane, London, N.W.1.

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FACULTY TOUR OF ITALIAN CLINICS

UNDER arrangements made by the Faculty of Ophthalmologists, twenty members, led by Dr. Robert Buxton, were able to make a tour of centres of ophthalmology in Italy, the clinics visited being those at Pavia, Genoa, Florence, Rome, Naples and Bologna. At each of these places the hospitality of the professors, and the opportunities for seeing the beauties of their cities, contributed greatly to the enjoyment of what was, in any case, an interesting and instructive tour.

At Pavia the party was welcomed by Professor Bietti and taken to a reception given by the Rector of the University of Pavia. In one of the courtyards of the University is a statue of Scarpa, the first Professor of Ophthalmology of Pavia.

At the Ophthalmic Clinic next morning Professor Bietti showed a number of cases on which keratoplasty had been performed, and demonstrated his technique. He also gave a lecture on Chemotherapy in Tuberculosis. He advised early administration of streptomycin (0·5 gm. b.d. subcutaneously) which may be given with

Promin in a 50 gm. course. He also referred to the use of Para-amino-salicylic acid (P.A.S.), which is well tolerated and rapidly absorbed. The bacteriostatic action of the drug may be obtained by a dosage of 10-15 gm. daily (divided into four doses) given in three week courses; it may be combined with streptomycin therapy. He also gave a second lecture on new trends in diathermy of the ciliary body.

Dr. Malone, First Assistant to Professor Maggiore at Genoa, demonstrated a patient wearing contact lenses with variable curve who was able to see 6/6, 6/9 and also read newsprint without additional correction. A visit was arranged to the San Giorgio Optical Company.

The Ophthalmic Clinic at Florence is a spacious modern building with an extensive out-patient department. Separate accommodation is provided for trachoma cases, but the number is stated not to be large at the present time. Professor Alajmo demonstrated his technique in several operations. He uses no speculum, lid sutures nor superior rectus sutures. Soft lens matter is removed by irrigation with a long-necked undine placed directly in the anterior chamber, the corneal flap being lifted with forceps.

Professor Cavara at Rome, gave a most interesting and instructive lecture on virus diseases of the uveal tract, including a useful classification of the various types. He recommends protein therapy, urotropine and plasma transfusions (especially the latter for sympathetic ophthalmia), using American dried plasma or, preferably, fresh plasma. The first (trial) dose of the latter is 100 c.c. intravenously, after two days 150-200 c.c. Total, five to six doses given at three day intervals. Milk injections have not produced good results.

His second lecture was on streptomycin and P.A.S. He gives 1·0 gm. of the former daily in two to four injections, for twenty to forty days, exceptionally up to sixty days, and observed the results to be satisfactory in twenty-nine cases of uveal tuberculosis, and brilliant in two cases of Parinaud's conjunctivitis. In two cases of choroiditis, one of juxta-papillary choroiditis and two of nodular irido-cyclitis he considered that healing was accelerated. In ocular tuberculosis produced by inoculating rabbits with T.B., he found that whereas streptomycin controlled the infection, P.A.S. had much less effect in checking the disease. The former encouraged fibrotic reaction, the latter cellular. In untreated controls caseation occurred. Professor Cavara then showed a number of cases including a retinal detachment due to cysticercus. This was one of eight cases received from one village, the source of infection being pork. He prefers to extract the cyst through a linear incision through sclera and uvea, which he makes as small as possible to avoid perforating

the retina at the edges of the cyst. Among other cases demonstrated were opacity of corneal stroma in two children, brother and sister, due apparently to congenital absence of Descemet's membrane, congenital atrophy of iris with chronic glaucoma, mobile cysts in anterior chamber following keratoplasty, lacrimation when chewing but not when crying, associated in this instance with Stilling-Turck syndrome, a case of Marcus Gunn's syndrome successfully treated by dividing the levator tendon of the lid and correcting the subsequent ptosis by a modification of Hess's operation, and finally a case of keratoconus, grafted, with the graft remaining flat but the surrounding cornea continuing to stretch.

The assistant professor, Dr. Missiroli, demonstrated his technique in operations for cataract, glaucoma and detached retina.

While in Rome a visit was paid to the Provincial Ophthalmic Hospital, a non-teaching establishment under the care of Dominican nuns. Professor Leonardi demonstrated various different techniques in cataract extraction, including intra and extra-capsular methods, the former with forceps, erisiphake, and diathermy coagulation in turn.

Members of the party will long remember the hospitality afforded to them by Professor Cavara during their stay in Rome, for during unoccupied moments they were not only enabled to see at least some of the famous buildings but also were present at the opera and enjoyed a sumptuous banquet given by Professor Cavara and his wife. Finally, they were honoured by an audience with His Holiness Pope Pius XII.

Much interest was aroused by the demonstrations of operative dexterity given by Professor Lo Cascio of Naples. Using two operating tables and four trained assistants he performed, without any appearance of haste, seven extra-capsular operations in fifty minutes, followed by three cyclodialyses and a diathermy operation for detachment of the retina. The technique he employs in the latter is careful localisation of the hole or holes by indirect ophthalmoscopy, and he inspects the fundus by this method again immediately after applying surface diathermy. The fluid is let out by one or more punctures at the site of the greatest ballooning. He has operated on many hundreds of detachments, and claims 75-80 per cent. successes.

Lastly, at Bologna Professor Di Marzio welcomed the party and gave an address on a subject in which he is particularly interested, that of cranial and cranio-orbital lesions which affect the visual neural paths, with especial reference to the chiasmatic syndrome. He showed records of cases with bitemporal, binasal and homonymous field defects. Slides were exhibited, showing the correlation between field changes and radiological appearances. Most of the

cases were treated with deep X-rays, and the results appear to have been good. (X-ray therapy is much used by Di Marzio in cases of inflammatory diseases of the eye. He gives 100 r. once or twice a week for such conditions as central serous retinitis, ulcerative keratitis and iridocyclitis).

His assistant, Dr. G. Cristini, gave a lecture on the radiographic investigation of obscure lesions of the optic nerves, and described his technique for inserting lipiodol into the paranasal sinuses, and also for injecting thorotrast into the carotid artery for cerebral arteriography.

Apart from the interest and instruction which this tour afforded from the professional point of view, and from the opportunity of seeing some of the most famous of the world's treasures in pictures, sculpture and architecture, no member of the party could fail to be impressed with the evident trouble taken by the various hosts on behalf of their visitors, a debt which it is hoped in some measure to repay here next year. Finally, a word of sincere appreciation for the unselfish and unflagging efforts by the party leader Dr. Robert Buxton, who planned the tour and spared no pains to make it the success it proved to be.

NOTES

Ophthalmological Society of Egypt

IN connection with the recent announcement of an award by the Ophthalmological Society of Egypt it is ruled that this prize is designated only for members of the Society, either in Egypt or abroad, who have been in practice less than 20 years.

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Appointment

DR. E. V. SRINIVASAN has been appointed Hon. Ophthalmic Surgeon to His Excellency the Governor General of India.

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Ophthalmological Society of Australia

MR. J. H. DOGGART and Mr. T. K. Lyle have been elected Honorary Members of the Ophthalmological Society of Australia.